CENTRAL VENOUS ACCESS DEVICE-ASSOCIATED SKIN IMPAIRMENT:
A PILOT STUDY COMPARING DRESSING TO NO-DRESSING IN ADULT
ALLOGENEIC STEM CELL TRANSPLANT RECIPIENTS

by

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Central venous access device-associated skin impairment: A pilot study comparing dressing to no-dressing in adult allogeneic stem cell transplant recipients

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Abstract

Central venous access device (CVAD) associated skin impairment (CASI) is common in adult allogeneic hematopoietic stem cell (HSCT) recipients, with symptoms ranging from mild erythema to ulceration. Not applying a dressing (no-dressing) to embedded tunneled CVAD (T-CVAD) exit sites may decrease CASI without increased risk of CVAD-related bloodstream infection (CRBSI), but evidence is lacking. This pilot study assessed the feasibility of conducting a large-scale longitudinal randomized controlled trial (RCT) comparing CASI and CRBSI between dressing and no-dressing in adult outpatient allogeneic HSCT recipients. Twenty-four participants were enrolled. Eligible participants had embedded T-CVADs, were within 35 to 60 days of transplant, and had achieved neutrophil engraftment. A modified Eastern Cooperative Oncology Group (ECOG) Skin Toxicity Scale was used to grade CASI at baseline and weekly for 6 weeks. The groups were compared using a two-way ANOVA for CASI episodes and a Fisher’s exact test for CASI episodes ≥ grade 2 and bloodstream infection. There was a statistically significant finding of fewer CASI episodes for the no-dressing group, and a statistically significant relationship between type of exit site care and CASI ≥ grade 2. Results of the statistical tests are estimates due to the small sample size. The major feasibility challenges were fewer eligible patients than expected and a high participation refusal rate (58%). The Modified ECOG Skin Toxicity Scale performed well; however, further testing is recommended. The study findings support the need for a RCT comparing CASI and CRBSI between dressing and no-dressing in the adult outpatient allogeneic HSCT setting.
Lay Summary

Allogeneic hematopoietic stem cell transplant (HSCT) is a treatment for blood disorders that involves the infusion of blood and immune cells from another person. Individuals undergoing allogeneic HSCT have a central venous access device (CVAD), a plastic tube inserted in a vein near the heart, so they can receive treatment. Skin around the CVAD exit site is typically covered with a dressing. Skin damage known as CVAD-associated skin impairment (CASI) can occur. Having no dressing might decrease CASI without increasing CVAD-related bloodstream infection risk, but evidence is lacking. The pilot study aimed to determine the feasibility of conducting a larger study. It involved randomizing 24 adult allogeneic HSCT recipients into dressing and no-dressing groups and then comparing CASI and bloodstream infection between the groups. CASI was assessed weekly for 6 weeks using a standardized assessment tool. The no-dressing group had less CASI. There is support for conducting a larger study.
Preface

This study was identified and designed by me in collaboration with Dr. Wendy Hall, Professor Emeritus, Faculty of Applied Sciences, School of Nursing, University of British Columbia, Dr. Fuchsia Howard, Assistant Professor, Faculty of Applied Sciences, School of Nursing, University of British Columbia, and Dr. Nicola Waters, Associate Professor, School of Nursing, Thompson Rivers University. All aspects of the conduct of the study were performed entirely by me, under the supervision of Dr. Wendy Hall, except for CASI assessments, which were also performed by some of my nursing colleagues at the Leukemia/BMT outpatient unit at Vancouver General Hospital. All data collection and analyses were carried out by me under the guidance of Dr. Wendy Hall. Ethics approval for this project was granted by the University of British Columbia Clinical Research Ethics Board, and hospital approval was granted by the Vancouver Coastal Health Research Institute, certificate of approval # H17-01002. This pilot study was registered with ClinicalTrials.gov prior to the commencement of enrollment. This study has yet to be published.
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# List of Abbreviations

ANC – Absolute neutrophil count  
AUC – Area under the curve  
CASI – CVAD associated skin impairment  
CBA – CASI boundary area  
CRBSI – Central venous catheter-related bloodstream infection  
CRLI – Catheter-related local infection  
CPGs – Clinical practice guidelines  
CVAD – Central venous access device  
CVC – Central venous catheter  
CHXSD – Chlorhexidine sponge dressing  
CHXG – Chlorhexidine gluconate  
DCF – Data collection form  
DTP – Differential time to positivity  
ECOG – Eastern Cooperative Oncology Group  
GVHD – Graft versus host disease  
HSCT – Hematopoietic stem cell transplantation  
ICDRG – International Contact Dermatitis Research Group  
ICU – Intensive Care Unit  
IRR – Inter-rater reliability  
IV – Intravenous  
LIP – Letter of Invitation to Participate  
ND – Needleless device  
PBSC – Peripheral blood stem cells
PQBC – Paired quantitative blood cultures
PICC – Peripherally inserted central catheter
RCT – Randomized controlled trial
REB – Regulatory Ethics Board
RRT – Regimen-related toxicity
SCST – Systemic corticosteroid therapy
T-CVAD – Tunneled and cuffed central venous access device
TBI – Total body irradiation
TEWL – Trans-epidermal water loss
TPN – Total parenteral nutrition
TRM – Treatment-related mortality
TSM – Transparent semipermeable membrane
VGH – Vancouver General Hospital
VCHA – Vancouver Coastal Health Authority
Glossary

**Absolute neutrophil count (ANC):** The number of neutrophils in a milliliter of blood, having a reference value of approximately 2 to 8 x 10⁹/L (Mosby, 2009).

**Allogeneic hematopoietic stem cell transplantation (HSCT):** A biological therapy used to treat malignant and non-malignant blood disorders, involving partial or complete ablation of the hematopoietic cells with high-dose chemotherapy, sometimes in combination with total body irradiation, followed by the infusion of hematopoietic stem cells from a healthy genetically matched donor (Ezzone, 2013).

**Autologous transplantation:** A biological therapy used to treat malignant and non-malignant blood disorders in which an individual’s own hematopoietic stem cells are collected, either by bone marrow harvest or a process known as apheresis, followed by the individual receiving high-dose chemotherapy and then the re-infusion of their previously collected hematopoietic stem cells (Ezzone, 2013).

**Bloodstream infection:** The presence of viable bacterial or fungal microorganisms in the bloodstream resulting in an inflammatory response causing changes to clinical, laboratory, and/or hemodynamic parameters (Viscoli, 2016).

**CASI boundary area (CBA) (as per Broadhurst and Tardiff (2016):** The area of skin within a 5 cm radius of a CVAD exit site.

**CVAD-associated skin impairment (CASI) as per Broadhurst and Tardiff (2016):** Skin abnormality within a 5 cm radius of the CVAD exit site due to mechanical, chemical, or microbiological injury that can be identified by one or more of the following signs and symptoms: erythema, edema, shiny skin, macular or papular lesions, maceration, folliculitis,
induration, pruritus, discomfort (pain), discharge, vesicle(s), bulla(e), skin tear(s), exfoliation, ulceration, and/or suspected or microbiologically confirmed local CVAD exit site infection.

**CVAD-related bloodstream infection (CRBSI):** A bloodstream infection arising from a CVAD rather than another source, based on clinical findings and/or laboratory methods with high sensitivity and specificity (O’Grady et al., 2011).

**CVAD-related localized infection (CRLI):** Localized infection occurring within 2 cm of a CVAD exit site and/or along the tunnel tract, characterized by tenderness, erythema, induration, and/or purulent discharge, with or without fever, and confirmed by microbiological testing (Mermel et al., 2009).

**Central venous access device (CVAD):** A catheter that terminates in the central venous vasculature, such that the distal tip is positioned in the lower one third of the superior vena cava at the junction of the superior vena cava and right atrium. This term includes short and long-term catheters, implanted ports, peripherally inserted central catheters, and tunneled central venous catheters (Phillips & Gorski, 2014).

**Data quality:** The accuracy and completeness of data collected (Polit, 2010).

**Differential time to positivity (DTP):** A method of determining CRBSI in which conventional blood cultures are drawn concomitantly through the CVAD and a peripheral site, with a diagnosis of CRBSI confirmed by a CVAD culture that becomes positive ≥ 2 hours prior to a positive peripheral culture (Safdar, et al., 2005).

**Dressing:** The practice of maintaining a dressing on a CVAD exit site at all times, including during showering (O’Grady et al, 2011).
*Eastern Cooperative Oncology Group (ECOG) skin toxicity scale:* A tool originally developed
to grade skin toxicity associated with chemotherapy and radiation regimens in the oncology
setting (ECOG CTC, 1997).

*Embedded T-CVAD exit site:* A tunneled CVAD exit site meeting the following criteria: (1) the
T-CVAD has been in situ a sufficient amount of time to allow subcutaneous tissue to become
embedded in the internal cuff, which typically takes 4 to 6 weeks from the date of insertion; (2)
the exit site suture has been removed; and (3) there is no evidence of CVAD movement. The
term “embedded exit site” is used synonymously in this document with the term “healed exit
site” (Mermel et al., 2009; O’Grady et al., 2011).

*Feasibility threshold:* In the context of this pilot study, this term is defined as the proportion of
actual events to total required events, established a priori, that needs to be exceeded or not
exceeded in order to predict successful completion of a large-scale study for the same population
and study procedures.

*Graft-versus-host-disease (GVHD):* A complication of allogeneic HSCT in which T cells from
the donor mount an immune response against the recipient’s tissues (Mitchell in Ezzone, 2013).

*Infection:* Infiltration and multiplication of microorganisms in body tissues, causing cellular
injury due to competitive metabolism, toxin production, intracellular replication, and/or antigen-
antibody interactions (Miller & Keane, 1983).

*International Contact Dermatitis Research Group (ICDRG) scale:* A tool used to both
differentiate between contact and irritant dermatitis, and to indicate the severity of contact
dermatitis reaction (Fregert, 1981).

*Inter-rater reliability (IRR):* The degree to which the ratings of two independent assessors are in
agreement (Polit, 2010).
**Missing data:** Values not available at the time of study analysis with respect to required data items established a priori (Little et al., 2012).

**Needleless device (ND):** A device attached to the lumen end of a CVAD that allows connection of IV tubing or drawing of blood without the need to open the system manually or access the system with a needle (Jarvis, 2009).

**Neutrophil engraftment:** The first day of achieving an absolute neutrophil count (ANC) of 0.5 x 10^9/L or greater for three consecutive measurements on different days (Walker et al., 2016).

**Neutrophils:** A type of white blood cell (WBC) that removes bacteria and cellular debris through phagocytosis and proteolysis (Mosby, 2009).

**Neutropenia:** An abnormally low number of neutrophils in the blood, usually characterized by a count < 0.5 x 10^9/L, which significantly compromises the body’s ability to fight infection (Mosby, 2009).

**No-Dressing:** The practice of leaving the exit site of a T-CVAD open to the air, including during showering (Lawrence, Seiler, Wilson, & Harwood, 2014).

**Outpatient HSCT clinic:** A specialized clinic designed for the care of medically stable HSCT recipients prior to and following transplant, in which patients are admitted for treatment and/or assessment, with visit duration ranging from 1 to 7 hours. Clinic operation is restricted to daytime and evening hours.

**Paired quantitative blood culture (PQBC):** A method of determining CRBSI in which quantitative blood cultures are drawn concomitantly through the CVAD and a peripheral site, with a diagnosis of CRBSI confirmed by the presence of microorganisms three to five times greater in the CVAD culture in relation to the positive peripheral culture (Safdar et al., 2005).
**Participant-dependent procedure:** A study procedure which participants are asked to follow during the course of a study, and which cannot be controlled by the researcher, but depends on the willingness and ability of the participant to comply. An example is a study requirement for a participant to take a specific dose of study medication at home at a specific time of day.

**Preparative regimen:** High-dose chemotherapy and/or total body irradiation (TBI) that is administered to an individual in order to fully or partially eliminate the hematopoietic cells in preparation for a hematopoietic stem cell transplant (HSCT) (Ezzone, 2013).

**Regimen-related toxicity (RRT):** Organ damage caused by chemotherapy and/or TBI given prior to HSCT (Bearman, et al., 1987).

**Seldinger technique (for CVAD insertion):** A method of percutaneous insertion of a catheter into a blood vessel, in which a needle is used to introduce a guide wire into the blood vessel, followed by the removal of the needle and then the threading of the central venous catheter over the guide wire into the vessel as far as required, and then the removal of the guidewire (Higgs, Macafee, Braithwaite, & Armstrong, 2005).

**Skin barrier function:** The ability of the skin to prevent harmful amounts of trans-epidermal water loss (TEWL) and to repel invasive microorganisms (Elias, 2008).

**Stratum corneum:** The outermost component of the epidermis, consisting of 15 to 20 layers of dead cells known as corneocytes, and an extracellular matrix consisting of lipids and proteins (Elias, 2008).

**Trans-epidermal water loss (TEWL):** The quantity of water that passes from inside the body through the epidermal layer to the surrounding atmosphere via diffusion and evaporation (Elias, 2008).
Treatment-related mortality (TRM): Death due to the effects of treatment of a disease rather than the disease itself (Ethier, Blanco, Lehrnbecher, & Sung, 2011).

Tunneled CVAD (T-CVAD): A surgically inserted CVAD where a portion of a catheter is placed in a subcutaneous tunnel between the exit site and entrance site. The exit site is where the catheter leaves the body, via an opening in the skin, typically in the anterior right chest region. The entrance site is where the catheter in the subcutaneous tract enters one of the large veins, usually the jugular or subclavian. T-CVADs have a synthetic cuff located 4 mm distal to the exit site, which becomes embedded with subcutaneous tissue approximately 4 to 6 weeks after insertion. The embedded cuff anchors the catheter to the body. This type of catheter is typically used in individuals requiring long-term IV treatment (Phillips & Gorski, 2014).
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Dedication

This thesis is dedicated to my husband Roger, and sons Nicholas and William. I offer my heartfelt gratitude to all of you. Many challenging hurdles along the way were made manageable because of your love, patience, kindness, and humour! This thesis could not have been completed without you. Thank-you for your faith in me.
Chapter 1: Introduction

1.1 Background

Allogeneic hematopoietic stem cell transplantation (HSCT) is a biological therapy used to treat malignant and non-malignant blood disorders. Approximately 31,926 allogeneic HSCTs are performed annually worldwide (Niederwieser et al., 2016). HSCT involves the full or partial ablation of the recipient’s hematopoietic cells using a preparative regimen of high-dose chemotherapy, sometimes in combination with total body irradiation (TBI), followed by the infusion of hematopoietic stem cells from a healthy genetically matched donor. The cells are infused via a central venous access device (CVAD), an intravascular catheter that terminates at the junction of the superior vena cava and the right atrium of the heart. The donor cells begin to reconstitute at approximately 2 weeks post-transplant, with neutrophil engraftment defined as the first day of achieving an absolute neutrophil count (ANC) of 0.5 x 10^9/L or greater for three consecutive measurements on different days (Walker et al., 2016). Unlike allogeneic HSCT, autologous HSCT involves the collection and infusion of an individual’s own hematopoietic stem cells. Serious complications are common with HSCT; therefore, this therapy is reserved for life-threatening diseases of the bone marrow resistant to pharmaceutical treatment alone.

Allogeneic transplant-related mortality (TRM) is approximately 26% (Gratwohl et al., 2005). The main causes of TRM are regimen-related toxicity (RRT), graft-versus-host disease (GVHD), and infection (Gratwohl et al., 2005; Tomblyn et al., 2009). RRT refers to organ damage caused by the preparative regimen. GVHD is an immune mediated response in which the donor cells react against the recipient (host) tissue. The greatest risk for infection occurs prior to neutrophil engraftment (Storek et al., 2008). Adult recipients have higher rates of
GVHD compared to children (60-70% versus 20-50%) (Baird, Cooke, & Schultz, 2010), and less vigorous regeneration of T-lymphocytes (MacKall et al., 1995). Adult recipients have a 48% probability of disease-free survival at five years post-transplant (Gratwohl et al., 2009).

In Canada, allogeneic HSCT is conducted at specialized HSCT centres. Inpatient care is typical from the onset of the preparative regimen until engraftment, and then care usually transitions to an outpatient HSCT Clinic. Ongoing blood product support, antimicrobial treatment, and immunosuppressive therapy are required until hematopoietic function is more robust and complications have diminished. The outpatient phase of care usually lasts 3 to 6 months, with visits occurring at intervals of 1 to 7 days. CVAD management is a major component of outpatient care.

CVADs are integral to allogeneic HSCT. The tunneled CVAD (T-CVAD) with three lumens is the most common in adults (Toro, Morales, Loberiza, Ochoa-Bayona, & Freytes, 2007). T-CVADs exit the body via a subcutaneous tunnel in the anterior chest and are anchored to subcutaneous tissue with an internal synthetic cuff. The main characteristic of an embedded T-CVAD exit site is a cuff that has become attached to surrounding subcutaneous tissue, a process which takes approximately 6 weeks to occur following T-CVAD insertion. The exit site suture is removed 4 to 6 weeks after insertion (Phillips & Gorski, 2014). Intravenous (IV) access via the T-CVAD occurs through a cap-like component called a needleless device (ND). CVADs are needed until approximately Day 100 post-transplant. Management of the T-CVAD involves routine lumen flushing with saline, ND replacement, and exit site dressing change. Allogeneic HSCT would not be possible without CVADs; however, there are associated risks.

Approximately 15% of patients with a CVAD experience a complication related to the device (Dix, Yeung, Rule, & Ma, 2012; Ivy et al., 2009). Bloodstream infection (BSI) arising
from the CVAD is one of the most common and most serious complications (O'Grady et al., 2011). The term **CVAD-related BSI (CRBSI)** is typically used to describe this situation; however, there is considerable variation regarding the specific criteria used by clinicians and researchers to confirm whether a BSI is linked to the CVAD or another source (O’Grady et al., 2011; Olson et al., 2004). CRBSI incidence density in the adult allogeneic HSCT population is estimated to range from 2.03 to 7.6 per 1,000 catheter days (Dix et al., 2012; Keeler et al., 2015). There is a lack of empirical evidence regarding the attributable mortality rate of CRBSI in adult HSCT recipients; however, rates ranging from 25% to 35% have been reported for Intensive Care Unit (ICU) patients (Pittet, Tarara, & Wenzel, 1988; Renaud & Brun-Buisson, 2001; Rosenthal, Guzman, Migone, & Crnich, 2003).

Neutropenia and duration of CVAD greater than 7 days have been found to increase the risk of CRBSI. (Howell, Walters, Donovitch, & Farr, 1995; Moro, Vigano, & Lepri, 1994; Raad, et al., 1993; Safdar, Kluger, & Maki, 2002). The role of increased exit site microbial colonization in the development of CRBSI in long-term CVADs is controversial. Some studies have found concordance between microorganisms cultured from the exit site and those cultured from blood drawn via the CVAD (Bjornson et al., 1982; Snydman et al., 1982), whereas Olson et al. (2004) did not. Research conducted by Raad et al. (1993) suggested that exit site colonization is not a major risk factor for CRBSI in CVADs in place greater than 7 days.

Given the potential morbidity and mortality associated with CRBSI, various strategies are utilized to prevent this complication. **Dressing** of the T-CVAD exit site is widely practiced as a means of preventing CRBSI (Keeler et al., 2015). O’Grady et al. (2011) recommended that a T-CVAD exit site should be dressed until embedded; however, optimal management of an embedded T-CVAD exit site is an unresolved issue (O’Grady et al., 2011; Ullman et al., 2015).
Approximately 60% of Canadian HSCT centres maintain a dressing on T-CVAD exit sites until catheter removal (Keeler et al., 2014); however, dressing a T-CVAD exit site confers risk. Dressings and antiseptics have been implicated in skin impairment proximal to the exit site (Benhamou et al., 2002; Rasero et al., 2000; Shivnan et al., 1991; Silveira, Bragga, Garbin, & Galvão, 2010).

1.1.1 CVAD-Associated Skin Impairment (CASI)

Broadhurst and Tardiff (2016) introduced the term CVAD-associated skin impairment (CASI) to signify skin impairment specifically affecting cutaneous tissue around CVAD exit sites. Broadhurst and Tardiff (2016) defined CASI as skin damage due to mechanical, chemical, or microbiological injury within 5 cm of the exit site. CASI consists of one or more of the following signs and symptoms: erythema, edema, shiny skin, macular or papular lesions, maceration, folliculitis, induration, pruritus, discomfort (pain), discharge, vesicle(s), bulla(e), skin tear(s), exfoliation, and/or ulceration. Suspected and microbiologically confirmed local skin infection at the exit site falls within the CASI syndrome (Broadhurst & Tardiff, 2016).

The presence of CASI reflects a compromise in skin barrier function - the ability of the epidermis to regulate transcutaneous evaporative water loss and prevent microbial infiltration (Duckney et al., 2013; Jinnestål, Belfrage, Bäck, Schmidtchen, & Sonesson, 2014; Waring, Bielfeldt, Mätzold, Wilhelm, & Butcher, 2011). Dressing adhesive, dressing material, and antiseptic solutions appear to be the primary factors contributing to CASI (Dykes, Heggie, & Hill, 2001; Maki, Alvarado, & Ringer, 1991; Visscher et al., 2009; Waring et al., 2009). Removal of adhesive dressings may result in stripping of the stratum corneum, the outermost layer of the epidermis (Dykes, et al., 2001). Antiseptics, such as chlorhexidine, alcohol, and povidone-iodine are associated with erythema of the skin (Maki et al., 1991; Visscher et al.,
The likelihood of skin impairment has been shown to increase as cumulative dressing change exposure increases (Matsumura et al., 2012; Tokumura et al., 2005). Evidence is lacking as to whether CASI increases the risk of CRBSI; however, studies of impaired skin barrier function suggest this may be the case (Duckney et al., 2013; Jinnestål et al, 2014; Larson et al., 1998).

CASI is a common clinical issue for allogeneic HSCT recipients. A mean frequency of 50% has been reported in pediatric HSCT recipients (Benhamou et al., 2002), and a frequency of 68% has been reported in a sample that included adult allogeneic HSCT recipients (Shivnan et al., 1991). In contrast, Timsit et al. (2009) reported a frequency of only 1.23% in medical and surgical ICU patients. Key differences between allogeneic HSCT recipients and ICU patients, described below, may explain the different CASI frequencies found in these studies.

Components of allogeneic HSCT preparative regimens and treatment-related conditions post-transplant may potentiate adverse skin reactions around CVAD exit sites. Busulfan, cyclophosphamide, and TBI, common components of HSCT preparative regimens, are associated with abnormalities in the nuclei of keratinocyte cells that persist for several weeks after transplant (Hymes et al., 1985; Simonen et al., 1998). Skin changes associated with transplant-related immunosuppressive therapy contribute to skin fragility and impaired wound healing (Gottlieb & Penneys, 1980; Hymes, et al., 1985; Poetker & Reh, 2010).

There are factors which may explain differences in CASI rates found within the allogeneic HSCT population. In a study of pediatric HSCT recipients, the rate of CASI was higher in participants who received a busulfan-containing preparative regimen (Benhamou et al., 2002), a finding relevant for adult allogeneic HSCT recipients given that busulfan is used in many, but not all, adult allogeneic HSCT preparative regimens. Allogeneic HSCT recipients
who develop skin GVHD and/or must commence corticosteroid therapy to treat GVHD may also be at increased risk of CASI (Fardet, Kassar, Cabane, & Flahault, 2007; Gottlieb & Penneys, 1980; Hymes, et al., 1985; Poetker & Reh, 2010). Exposure to busulfan, skin GVHD, and systemic corticosteroid therapy (SCST) may be important risk factors with respect to CASI in allogeneic HSCT recipients.

### 1.1.1.1 Strategies to Decrease CASI

Extending the dressing change interval has been studied as a strategy to decrease CASI. Rasero et al. (2000) found less CASI with a 5-day change interval in comparison to a 2-day interval in a sample of autologous and allogeneic HSCT recipients; no difference was found between a 5-day and 10-day interval. In a study of pediatric allogeneic HSCT recipients, Benhamou et al. (2002) found less CASI with a 15-day interval in comparison to a 4-day interval. As less CASI was found with a longer dressing change interval in two of three comparisons, it is possible that CASI could be decreased by leaving the T-CVAD exit site open to the air, an approach known as no-dressing. No-Dressing would reduce exposure to dressings and antiseptics, just as increasing the dressing change interval decreased exposure.

Approximately 40% of Canadian HSCT centres practice no-dressing for embedded T-CVAD exit sites (Keeler et al., 2014), including Princess Margaret Hospital HSCT centre, the largest HSCT centre in Canada (personal communication, Incekol, 2016); however, these centres have not published their CASI rates.

### 1.1.1.2 Dressing Versus No-Dressing

Five studies have compared dressing and no-dressing in adult patients with long-term CVADs; however, the focus of these studies was a comparison of infection rather than CASI (Chambers et al., 2005; Keeler et al., 2015; Nagai et al., 2012; Olson et al., 2004; Petrosino,
Becker, & Christian, 1988). Of these five studies, three compared CRBSI. Equivalence was found between dressing and no-dressing groups (Keeler et al., 2015; Nagai et al., 2012; Olson et al., 2004). A large-scale definitive prospective RCT has not been conducted comparing both CASI and CRBSI rates between dressing and no-dressing groups.

1.2 Problem Statement

For outpatient adult allogeneic HSCT recipients, CASI is a common complication that contributes to patient discomfort and possibly increased infection risk. There is a paucity of research focused on strategies to prevent this clinical problem. No-Dressing may be an effective way to decrease CASI in outpatient adult allogeneic HSCT recipients with embedded T-CVAD exit sites, but evidence is required. An adequately powered prospective RCT is needed in this population to determine if no-dressing is superior to dressing with respect to decreasing CASI without increasing CRBSI. A pilot study comparing dressing and no-dressing is an important first step in evaluating the feasibility of completing a high quality large-scale prospective RCT.

1.3 Significance

CASI is a common clinical problem in adult allogeneic HSCT recipients. More than half of HSCT centres in Canada maintain a dressing on embedded T-CVAD exit sites (Keeler, 2014); however, this practice is not benign. CASI is associated with pain and emotional distress (Benhamou et al., 2002; Lawrence et al., 2014). There are also cost implications. CVAD dressings are changed every 2 to 7 days (Gorski, Hadaway, Hagle, McGoldrick, & Meyer, 2016; O’Grady et al., 2011). A dressing takes approximately 20 minutes to change, and supply cost is $38.56 per dressing change (Keeler et al., 2015). Dressing changes are more complex and costly in the context of CASI (Broadhurst & Tardiff, 2016). No-Dressing may decrease CASI without increasing CRBSI. This is a key consideration given that the primary rationale for dressing
embedded CVAD exit sites is CRBSI prevention. A change in practice to no-dressing has the potential to reduce nursing time devoted to CVAD care in the outpatient HSCT setting, reduce health care costs, and decrease patient discomfort without increasing infection risk.

1.4 Purpose

The purpose of the pilot study was to evaluate the feasibility of conducting a prospective longitudinal randomized controlled trial (RCT) to compare dressing and no-dressing groups with respect to CASI episodes, CASI severity, and CRBSI rate in outpatient adult allogeneic HSCT recipients with embedded T-CVAD exit sites. The pilot study was designed to function as a smaller version of a full-scale RCT so that the following elements could be assessed for feasibility: enrollment, randomization, data quality, participant withdrawal, outcome measures, and data analysis (Kasenda et al, 2014; Leon, Davis, & Kramer, 2011).

1.5 Research Questions and Hypotheses

There were four research questions and hypotheses associated with the study. All questions were specific to outpatient adult allogeneic HSCT recipients with T-CVADs.

**Primary Research Question:**

Will there be fewer CASI episodes for the no-dressing group than the dressing group?

Hₐ: There will be significantly fewer CASI episodes for the no-dressing group in comparison to the dressing group.

**Secondary Research Questions:**

**Secondary question 1:**

Will there be a relationship between type of exit site care (dressing or no-dressing) and CASI ECOG grade > 2?
**H₀**: There will be a significant relationship between type of exit site care and CASI ECOG grade ≥ 2.

**Secondary question 2:**
Will there be more CASI episodes at the last study visit than at baseline for the dressing group?

**H₀**: There will be significantly more CASI episodes at the last visit in comparison to baseline for the dressing group.

**Secondary question 3:**
Will there be a relationship between type of exit site care (dressing or no-dressing) and CRBSI?

**H₀**: There will be no significant relationship between type of exit site care and CRBSI.

### 1.6 Study Objectives

Specific objectives of the pilot study are described below.

1. Evaluate the following enrollment characteristics: (1) enrollment rate, (2) time to complete enrollment, and (3) reasons for non-enrollment.

2. Evaluate the following aspects of CASI data quality: (1) CASI assessment completion rate, (2) reasons for non-completion, and (3) CASI assessment consistency.

3. Evaluate the following aspects of data quality in general: (1) data error rate, (2) missing data rate, (3) type of missing data, and (4) reason(s) for missing data.

4. Evaluate the following participant withdrawal characteristics: (1) withdrawal rate, and (2) reasons for withdrawal.

5. Obtain feedback from participants regarding their compliance with study procedures.

6. Obtain feedback from participants regarding their study experience.

7. Describe and compare baseline participant characteristics in the two study groups to determine the effectiveness of the randomization procedure in balancing the groups.
8. Calculate frequencies of dressing regimen characteristics, CRBSI incidence density, CASI grades, and rate of participant preference for no-dressing post-study to: (1) identify problems with data collection and (2) generate preliminary information for future study planning.

9. Conduct statistical testing of the study hypotheses to: (1) identify problems with data collection, outcome measures, and/or statistical testing methods; and (2) generate estimates of significance, effect size, and variability for future study planning.

1.7 Summary

CASI is a significant problem with respect to the allogeneic HSCT population. The preparative regimen, GVHD, and cumulative dressing change exposure may be key factors in the development and severity of CASI in the allogeneic HSCT population. Adult HSCT recipients receiving follow-up care in the outpatient setting are a distinct sub-group of allogeneic HSCT recipients. No-Dressing as a strategy to decrease CASI has not been studied in outpatient adult allogeneic HSCT recipients, despite evidence that suggests this HSCT sub-population may be at high risk for CASI. In addition, further evidence is needed regarding the risk of CRBSI for no-dressing. The purpose of this pilot study was to determine the feasibility of conducting a large-scale prospective longitudinal RCT comparing CASI and CRBSI between dressing and no-dressing groups in outpatient adult allogeneic HSCT recipients. In the next chapter a summary of relevant scientific evidence is presented.
Chapter 2: Literature Review

2.1 Introduction

Chapter 2 presents a critical review of scientific literature relevant to the comparison of using a dressing and not using a dressing with respect to CASI and CRBSI in adult outpatient allogeneic HSCT recipients with embedded T-CVAD exit sites. The chapter begins with a description of the parameters for the literature review.

2.2 Search Methods

The literature search involved the identification of studies relevant to CASI, CRBSI and no-dressing in outpatient adult allogeneic HSCT recipients with embedded T-CVAD exit sites. Articles were reviewed in full if the following criteria were met: (1) published in a peer reviewed English language journal; (2) original research; (3) relevant to CASI, CVAD-related infection, and/or dressing versus no-dressing; and (3) study sample comprised of adult allogeneic HSCT recipients with CVADs and/or other relevant samples. The literature search occurred between January 15, 2016 and March 1, 2017.

Multiple searches using the Google Scholar search engine were conducted. Searches were repeated using PubMed, CINAHL, and the Cochrane Databases of Systematic Reviews and Central Register of Controlled Trials, in order to obtain a comprehensive selection of peer reviewed publications. Each search involved a combination of two or more of the following terms joined by Boolean operators: central venous access device(s), CVAD(s), central venous catheter(s), CVC(s), CVAD-associated skin impairment, CASI, skin damage, skin toxicity, skin stripping, stratum corneum, skin barrier function, cutaneous, epidermal, dressing adhesive, chlorhexidine, central venous catheter infection, bloodstream infection, CRBSI, high-dose
chemotherapy, TBI, radiation, busulfan, cyclophosphamide, fludarabine, skin toxicity, GVHD, immunosuppressive therapy, prednisone, cyclosporine, tacrolimus, steroids, corticosteroids, skin changes, thinning skin, dressing, no-dressing. Publication titles generated by each search were visually scanned. If a title indicated potential eligibility, the abstract was obtained for review. If the abstract confirmed eligibility, the publication was obtained for full review. Additional eligible publications were identified via reference tracking and citation analysis.

2.3 Synthesis of Evidence

2.3.1 CASI

2.3.1.1 Identification and Grading of CASI

A specific tool for identifying and grading CASI has not been published. The ECOG Skin Toxicity Scale (v. 1997), originally developed to grade RRT in oncology trials, has been used successfully in three CASI studies (Orsino et al., 2009; Rasero et al., 2000; Silveira, et al., 2010). Timsit et al. (2009) and Mimoz et al. (2015) used the ICDRG scoring system (Fregert, 1981), a method of distinguishing between irritant and allergic contact dermatitis, whereas Benhamou et al. (2002) and Shivnan et al. (1991) developed study-specific scales. Details of these methods are shown below in Tables 2.1 to 2.4. A common feature of these tools is subjective visual assessment, rather than objective instrument-based assessment. There are strengths and weaknesses with all of these tools. The Shivnan et al. tool was found to demonstrate inter-rater reliability (IRR) ranging from 66% to 100% whereas Benhamou et al., Rasero et al., and Timsit et al. did not address IRR. In terms of weaknesses, the ICDRG, and Benhamou et al.’s, and Shivnan et al.’s tools do not account for the full gamut of CASI signs and symptoms. The ECOG Skin Toxicity Scale (v. 1997) includes the greatest range of CASI signs and symptoms.
### Table 2.1 ECOG Skin Toxicity Scale (ECOG, 1997)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Scattered macular or papular eruption or asymptomatic erythema</td>
</tr>
<tr>
<td>2</td>
<td>Scattered macular or papular eruption or erythema with pruritus or other associated symptoms</td>
</tr>
<tr>
<td>3</td>
<td>Generalized symptomatic macular, papular or vesicular eruption</td>
</tr>
<tr>
<td>4</td>
<td>Exfoliative dermatitis or ulcerating dermatitis</td>
</tr>
</tbody>
</table>

### Table 2.2 ICDRG Scoring System (Fregert, 1981)

| ? + | Doubtful reaction; faint erythema only                                         |
| + (1+) | Weak (non-vesicular) positive reaction; erythema, infiltration and possibly papules |
| ++ (2+) | Strong (vesicular) positive reaction; erythema, infiltration, papules, vesicles |
| +++ (3+) | Extreme positive reaction; bullous reaction |
| − (0) | Negative reaction                                                             |
| IR   | Irritant reaction                                                             |

### Table 2.3 Skin Toxicity Scale (Benhamou et al., 2002)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>1</td>
<td>Slightly inflamed skin</td>
</tr>
<tr>
<td>2</td>
<td>Minor cutaneous lesions, dressing difficult to remove</td>
</tr>
<tr>
<td>3</td>
<td>Lesions reaching the periphery of the dressing</td>
</tr>
<tr>
<td>4</td>
<td>Cutaneous lesions to such an extent that the usual dressing cannot be used</td>
</tr>
</tbody>
</table>

### Table 2.4 CVAD Exit Site Assessment (Shivnan et al., 1991)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin irritation</td>
<td>Yes or No</td>
</tr>
<tr>
<td>Erythema</td>
<td>0, 1, 2 or 3</td>
</tr>
<tr>
<td>Pain</td>
<td>0, 1, 2 or 3</td>
</tr>
</tbody>
</table>

#### 2.3.1.2 CASI Frequency

Evidence suggests that allogeneic HSCT recipients experience CASI more than other patient populations, although the body of evidence is small (Benhamou et al., 2002; Mimoz et
al., 2015; Orsino et al., 2009; Rasero et al., 2000; Shivnan et al., 1991; Silveira et al., 2010; Timsit et al., 2009). Comparisons between studies are problematic due to different study designs, variations in follow-up length, heterogeneous study samples, different exit site care regimens, lack of information regarding CVAD duration at enrollment, different approaches of reporting measurement frequency, and/or different methods of CASI measurement. Differences in eligibility criteria regarding baseline CASI also limit comparison between studies; however, all studies cited identified some degree of CASI.

Timsit et al. (2009) compared conventional dressings and chlorhexidine sponge dressings (CHXSD) in 1636 adult acute medical and ICU patients with a variety of intravascular catheters, including arterial catheters and different CVAD types. Participants were initially randomized to either a “CHXSD” cohort or a “conventional dressing” cohort. The participants in each cohort were then randomized to either 3-day or 7-day dressing change intervals and were followed for a median of 11 days (IQR, 5-22). The primary focus of this study was a comparison of catheter-related infection outcomes; however, CASI was assessed at each of the 12,882 dressing changes that occurred during the study using the ICDRG scoring system (Fregert, 1981). The authors reported skin reactions at 1.23% of dressing changes for all groups combined. Mimoz et al. (2015) also used the ICDRG scoring system to evaluate CASI. In this study CASI was analyzed as a secondary endpoint in a sample of adult ICU patients with different types of short-term CVADs (n = 2349). Participants were randomized to four groups. Chlorhexidine-alcohol and povidone-iodine-alcohol with scrubbing and without were compared. Median days of follow-up for each group was 8 days in the Mimoz study according to the details of the protocol published by Goudet et al. (2013). Mimoz et al. reported that 13% of all participants had “redness” at the exit site when the CVAD was removed.
Orsino et al. (2009) reported CASI frequency in a sample of 435 adult hematology and oncology patients with different types of CVADs. The ECOG skin toxicity scale (v. 1997) was used to measure CASI. Patients with CASI $\geq$ grade 2 were excluded from participating in the study. The prevalence of no CASI and grade 1 CASI at baseline for enrolled participants was equal to 97.01% and 2.99% respectively. Participants had between three to five dressing changes and dressing change intervals ranged from 3 to 10 days. It is unclear if any participants were allogeneic HSCT recipients. Six different sizes of a highly permeable transparent dressing were evaluated but not compared. At the end of the study, 5.06% of participants demonstrated a worsening of CASI from none or grade 1 up to grade 2 or 3 CASI. Orsino et al. did not explain if the findings of grades 2 and 3 CASI at the end of the study evolved from grade 0 or grade 1.

The highest frequencies of CASI have been found in studies that included allogeneic HSCT recipients. Shivnan et al. (1991) reported erythema in 68% of participants in a study of 98 patients who had undergone either autologous or allogeneic HSCT. Participants were randomized to either gauze or a Tegaderm™ transparent adherent dressing. CASI was assessed daily during the 30-day study using a study-specific assessment tool. The method used to calculate the reported frequencies of CASI symptoms was unclear. Silveira et al. (2010) used the ECOG skin toxicity scale (v. 1997) to assess CASI in a case study of 10 allogeneic HSCT recipients with a mean follow-up of 28 days. In this study 60% of participants experienced some degree of CASI during the time they were followed. Participants in the Shivnan et al. and Silveira et al. studies had either gauze or transparent semipermeable (TSM) dressings. Shivnan et al.’s study had methodological strengths such a larger sample size ($N = 98$) and formal evaluation of IRR with respect to the study-specific tool used. Although the Silveira et al. study was a small case series with only 10 participants, variables were well-defined, assessors were
trained to maximize IRR, and the sample was comprised solely of allogeneic HSCT recipients. Rasero et al. (2002) reported relatively low frequencies of CASI in their study of autologous and allogeneic HSCT recipients \( (N = 259) \). Their study participants were first separated by type of catheter (tunneled or non-tunneled), with 160 in the tunneled CVAD group and 99 in the non-tunneled CVAD group. In the T-CVAD group participants were randomized to dressing change intervals of 5 days (group A1) or 10 days (group A2), and in the non-T-CVAD group, to either 2 days (group B1) or 5 days (group B2). This was a longitudinal study, although neither median or mean days of follow-up were reported. Instead, the total number of dressing changes for each group were reported and ranged from 200 to 415. Rasero et al. reported CASI frequencies of 14% (group A1), 13% (group A2), 25% (group B1), and 34% (group B2), with total dressing changes in each group equal to 415, 280, 293, and 200 respectively.

While these interventional studies provide some insight into the extent of CASI in allogeneic HSCT recipients in comparison to other populations, the methods of calculating and reporting CASI frequency vary to the point where it is difficult to draw meaningful conclusions. The lack of clear evidence regarding CASI incidence and prevalence in general and for allogeneic HSCT recipients represents a major gap in the literature.

### 2.3.1.3 CASI Severity

In terms of severity, mild CASI appears to be more common than moderate or severe CASI in HSCT recipients, although comparisons of study results are hindered by the limitations discussed above. In a sample of adult autologous and allogeneic HSCT recipients, Rasero et al. (2000) found ECOG (v. 1997) grade 1 CASI was present at 9%, 12%, 20% and 31% of dressing changes for four different dressing change interval groups, whereas grade 2 CASI ranged from 1.7% to 5%, and grade 3 CASI ranged from 0% to 0.3%; no grade 4 CASI was reported. The
number of new cases of CASI that developed or cases of a worsening grade of CASI were not reported in this longitudinal study.

In a pediatric study of primarily autologous HSCT recipients, CASI was compared between a 15-day dressing change group and a 4-day group, with a mean of seven dressing changes in the 15-day group and 12 in the 4-day group (Benhamou et al., 2002). CASI was assessed at each dressing change using the study-specific scale shown in Table 2.3. The incidences of each grade of skin toxicity that developed during this longitudinal study were reported by group. Grade 1 CASI was the most frequently reported type of CASI (Benhamou et al., 2002). With respect to the overall distribution of CASI incidence by grade, the following incidences were reported for the 15-day and 4-day groups respectively: no CASI (37% and 18%); grade 1 (48% and 39%); grade 2 (11% and 34%); grade 3 (2% and 7%); and grade 4 (2% and 2%) (Benhamou et al., 2002). In the Silveira et al. (2010) study the maximum ECOG grade of CASI experienced by each participant was reported. In contrast to Rasero et al. and Benhamou et al., (2002), Silveira et al. reported severe CASI (i.e. ECOG grade 4) in 40% of their study participants; although this finding may have reduced validity due to the extremely small sample size ($N = 10$).

### 2.3.1.4 CASI Pathophysiology

#### 2.3.1.4.1 Dressings

Dressings appear to play a major role in CASI. Gauze, polyurethane, and silicone dressings are the most commonly used CVAD dressings (Broadhurst, Moureau, & Ullman, 2016; Ullman et al., 2015). A small body of evidence exists regarding the impact of dressings on skin integrity. Although most studies have been conducted in healthy volunteers, findings are relevant to the adult allogeneic HSCT population with respect to the mechanism of CASI. Dykes
et al. (2001), Waring et al. (2011), and Matsumura et al. (2012) assessed five, six, and eight
different dressings respectively in samples of healthy volunteers. Dressings and controls were
allocated to test sites by randomization. Stratum corneum stripping was measured by
quantitative instrument-based methods. Dykes et al. employed optical density measurement,
Waring et al. used trans-epidermal water loss (TEWL) measurement and digital imaging
technology, and Matsumura et al. relied on digital imaging technology. Waring et al. also
collected and analyzed data obtained via subjective visual assessment. All of these researchers
found evidence of damage to the stratum corneum with the majority of dressings tested. Specific
findings are discussed below.

Dykes et al. (2001) reported statistically significant differences in the stratum corneum at
baseline and after dressing removal for all dressings tested \( (p < .0001) \). Waring et al. (2011)
found elevated TEWL for five of six dressings tested, with statistically significant increases from
baseline ranging from \( 5g/m^2/h \) to \( 28g/m^2/h \) \( (p < .001) \), although participants reported minimal
reactions regarding pruritus, burning, and skin tightness. Matsumura et al. (2012) found stratum
corneum stripping occurred with all eight dressings tested; however, the extent varied between
dressings. Mean desquamated area ranged from 0.37% to 12.97%, with some differences
between dressings reaching statistical significance (Matsumura et al., 2012). All of these studies
used randomization to determine test and control sites and the incorporation of laboratory-based
methods that offered objective quantitative measurement of cellular-level changes; however,
there were limitations with their methods. Variations in equipment and computer software
between studies, differences in the experience level of equipment operators, and fluctuating
environmental conditions may have confounded the results. Findings from these studies were
also limited by small sample sizes ranging from 10 to 22 participants. In addition, two of the
research teams (Dykes et al., 2001 and Waring et al., 2011) received grants from Mölnlycke Healthcare, a company that manufactures some of the dressings tested in these studies, which may have introduced some study bias.

Zillmer, Agren, Gottrup, and Karlsmark (2006) evaluated the effects of four different dressings on the stratum corneum in a sample of 45 adult patients with either open or healed venous leg ulcers by measuring TEWL and electrical conductance before and after dressing removal. Skin barrier impairment was found with hydrocolloid dressings but not with polyurethane and silicone dressings. These findings are in contrast to those of Waring et al. (2011) and Matsumura et al. (2012) who reported that all dressings tested, including silicone and polyurethane, were associated with skin barrier impairment. In summary, authors of studies have reported impairment of the stratum corneum with a wide range of dressings, although some dressings were more damaging than others. Studies evaluating no-dressing as a means to decrease CASI are needed in adult allogeneic HSCT recipients given evidence that the dressing of T-CVAD exit sites likely contributes to skin breakdown in some individuals.

2.3.1.4.2 Antiseptic Solutions

Antiseptics used to clean CVAD exit sites also contribute to CASI, but the relationship is less clear than for dressings. Chlorhexidine 2% in isopropyl alcohol 70% is the most widely used antiseptic solution with respect to CVAD exit site care (Broadhurst et al., 2015). Chlorhexidine without alcohol, alcohol 70%, and povidone-iodine 10% are common alternatives (Broadhurst et al., 2015; Maki et al., 1991). There is no published data regarding the relationship between antiseptic solutions and CASI in adult allogeneic HSCT recipients; however, a small body of other relevant evidence can be found in the literature.
Tupker, Schuur, and Coenraads (1997) compared irritation of forearm skin between six antiseptic solutions in a sample of 20 adults without skin conditions. Minimal and statistically equivalent irritation was found with respect to chlorhexidine 4%, chlorhexidine 0.5% in ethanol 70%, and povidone-iodine 10%. Maki et al. (1991) reported erythema at the CVAD exit site as a secondary outcome in an RCT that compared three different antiseptic solutions with respect to CVAD-associated infection. The sample comprised 668 adult surgical ICU patients with various types of CVADs. The antiseptics were applied in conjunction with CVAD exit site dressing changes. Gauze and tape dressings were used and changed every 48 hours. Frequency of erythema in the povidone-iodine 10%, isopropyl alcohol 70%, and aqueous chlorhexidine gluconate 2% groups was 28.3%, 39.2%, and 45.3% respectively. The authors reported that erythema frequency was statistically equivalent between groups; however, the $p$ value and power were not provided, creating uncertainty as to whether erythema was truly equivalent.

A similar study was conducted by Vallés et al. (2008). This study also involved the enrollment of a large sample of adult ICU patients ($N = 420$). Equivalent skin inflammation was found regarding 10% aqueous povidone-iodine, 2% aqueous chlorhexidine gluconate, and 0.5% chlorhexidine alcohol gluconate ($p \geq .20$). In contrast, Mimoz et al. (2015) found statistically greater erythema with povidone-iodine 5% in alcohol in comparison to chlorhexidine 2% in alcohol, with an incidence rate of 15% and 12% respectively ($p = .01$). Loewenthal, Dobson, and Boyle (2016) found greater risk of skin irritation with chlorhexidine 2% in comparison to chlorhexidine 1% (Incidence rate ratio, 3.10, 95% CI, 1.34-7.24; $p = .008$) in a retrospective observational study of 2,628 patients receiving outpatient IV antibiotic therapy. The key conclusion from these studies is that all antiseptics have the potential to irritate the skin; however, it is still unclear which antiseptics are the most damaging. Further research is needed.
in adult outpatient allogeneic HSCT recipients to determine the magnitude of the relationship between antiseptics and CASI in this unique population.

A study by Visscher et al. (2009) is one of the few to evaluate the relative difference between dressings and antiseptic solutions with respect to skin impairment. This study involved 14 neonates with peripherally inserted central catheters (PICCs). Similar to allogeneic HSCT recipients, neonates have fragile skin and sub-optimal immune function. Erythema and skin dryness were compared between three within subject skin site groups using ANOVA. The three skin sites were: (1) PICC exit site skin, exposed weekly to both 2% chlorhexidine in 70% alcohol (CHXG) and TSM dressing changes; (2) A contralateral skin site, exposed weekly to TSM dressing changes; and (3) An adjacent skin site, not exposed to either CHXG or dressing changes. Erythema and dryness were assessed visually 2 minutes after antiseptic application and were measured with two different scales of 7 and 11 increments respectively. Assessments were conducted prior to PICC insertion and then weekly for 3 weeks. Statistically significant differences between the PICC exit site and dressing site were found at Week 1, but only for erythema and dryness ($p < .001$). The results of this study provide insight into the relative effects of TSM dressings and CHXG in a population with fragile skin. This study suggests antiseptic solution may be a less influential factor in CASI than dressings; however, the lack of a CHXG only group and the very small sample size are considerable limitations.

2.3.1.4.3 Cumulative Exposure to Dressings and Antiseptics

Cumulative exposure may be a moderating factor with respect to CASI. Tokumura et al. (2005) investigated repetitive application of general medical adhesive tape in seven healthy volunteers. Although adhesive tape is not equivalent to CVAD dressing adhesive, findings from the Tokumura et al. study are relevant to the mechanisms of CASI. Adhesive tape was applied
every day for 4 hours for 4 days in the summer, and for 8 days in the winter. A positive linear relationship between TEWL and area ratios of cumulative stripped corneocytes was found, with Pearson’s correlation coefficient equal to .985 and .834 for winter and summer respectively. Destruction of skin surface topography, measured by the replica method, was found to be greater in winter than summer. Spearman’s coefficient for area ratio of stripped corneocytes and deepened skin furrows was .910 for winter and .410 for summer. Interpretation of variations between findings in winter and summer is problematic as the length of treatment periods differed, and findings in general are limited by the small sample size. Waring et al. (2011) also found that cumulative dressing change exposure resulted in greater stratum corneum damage. A significant increase in TEWL was found after five dressing changes over a 15-day period compared to the first dressing change. The area under the curve (AUC) was analyzed using repeated measures ANOVA ($p < .001$).

The results of some clinical studies are consistent with the laboratory studies described above because more skin damage was found with greater exposure to dressing changes. In the Timsit et al. (2009) study, the number of dressing changes was relatively low in all the study groups (a median of 4 (IQR, 3-6) and 3 (IQR, 2-5) in the 3-day and 7-day groups respectively) with an overall CASI frequency of 1.23%. Total number of dressing changes per participant ranged from three to five in the Orsino et al. (2009) study, with CASI incidence reported as 5.06% when moderate and severe CASI were combined at the end of the study. In contrast, Silveira et al. (2010) reported a CASI frequency of 60% in their study which involved more
dressing changes per participant than in the Timsit et al. and Orsino et al. studies. The estimated average number of dressing changes per participant in the Silveira et al. study was eight\(^1\).

In a prospective RCT of 98 pediatric and adult autologous and allogeneic HSCT recipients, gauze dressings were compared to Tegaderm\textsuperscript{TM} transparent adhesive dressings (Shivnan et al., 1991). Gauze dressings were changed daily and transparent dressings were changed every 4 days. Although follow-up was only 30 days, cumulative dressing exposure was high with a mean of 10.7 and 26 dressing changes in the transparent and gauze dressing groups respectively. A relatively high frequency of CASI was reported for both groups combined (58\%). Significantly greater skin irritation was found with gauze dressings in comparison to transparent dressings (\(t = -3.6323, df = 76.0, p < .005\)). While the authors attributed this difference to dressing type, it is quite possible this difference was due, at least in part, to greater cumulative dressing change exposure in the gauze group.

Research regarding CASI and cumulative dressing change exposure is relevant for outpatient allogeneic HSCT recipients given the lengthy duration of CVAD placement and high risk of CASI in this population (Shivnan et al., 1991; Silveira et al., 2010). Studies with short follow-up (i.e. < 5 dressing changes) may not demonstrate the true impact of dressings and antiseptics. Higher CASI frequency occurred in studies with more dressing changes (Shivnan et al., 1991; Silveira, et al., 2010). The Shivnan et al. (1991) and Silveira et al. (2010) study samples also included allogeneic HSCT recipients. It is unclear whether the relatively higher CASI frequencies were due to greater dressing change exposure, differences in dressing types

\(^{1}\text{Based on the standard intervals for gauze dressing change (every 48 hours) and polyurethane dressing change (every 7 days) and the median number of days reported for each of these dressing types in the study results (13 days for gauze and 15 days for polyurethane) (Silveira, et al. 2010).}\)
and/or antiseptics used, or factors specific to the allogeneic HSCT population. It is possible the impact of repeated dressing application and removal is more pronounced in allogeneic HSCT recipients in view of skin changes due to the preparative regimen, immunosuppressive therapy, and skin GVHD. It is important to conduct further studies regarding CASI in adult allogeneic HSCT recipients given evidence this patient group may be at greater risk.

2.3.1.4.4  Risk Factors for CASI in Allogeneic HSCT Recipients

Some transplant-related factors may increase the risk and/or severity of CASI for allogeneic HSCT recipients. Preparative regimens containing busulfan are associated with a higher rate of CASI than non-busulfan containing preparative regimens (Benhamou et al, 2002). In a study of 113 pediatric HSCT recipients, Benhamou et al. (2002) found participants who received a preparative regimen containing busulfan had a significantly higher rate of CASI than those who did not receive busulfan (logrank test, \( p = .05 \)). Although this was a pediatric study and included a mix of autologous and allogeneic HSCT participants, the findings are relevant for adult allogeneic HSCT recipients given the common, but not exclusive, use of high-dose busulfan in adult allogeneic preparative regimens. Cutaneous damage at the cellular level has been identified following cyclophosphamide and/or TBI (Hymes et al., 1985; Simonen et al., 1998); however, no studies could be located that examined the relationship between these HSCT conditioning therapies and CASI. Skin GVHD, one of the most prevalent complications following allogeneic HSCT, can weaken the integrity of the skin. (Chaudhuri & Smoller, 1992; Hymes et al., 1985; Shulman et al., 1978) Similarly, long-term therapy with systemic corticosteroids can impair wound healing and skin barrier function (Dostal & Gamelli, 1990; Huscher et al., 2009). Clinical evidence in allogeneic HSCT recipients regarding the relationship between CASI and skin GVHD and/or systemic corticosteroid therapy is lacking. Current
evidence supports the need to consider busulfan exposure when designing studies that compare rates and/or severity of CASI in allogeneic HSCT recipients (Benhamou et al., 2002). The role of other conditioning chemotherapies, e.g., TBI, skin GVHD and/or corticosteroid exposure, is less clear. Given the limitations of a pilot study and available evidence, the most appropriate stratification factor with respect to CASI would be busulfan exposure (yes/no).

2.3.1.4.5 Skin Barrier Function and Infection

Intact skin is a critical component of infection prevention, particularly in immunocompromised individuals (Wolfson, Sober, & Rubin, 1985). The relationship between CASI and CVAD-related infection has not been studied; however, a diverse body of evidence exists regarding the consequences of impaired epidermal barrier function and infection in general. Jinnestål et al. (2014) studied the relationship between impaired skin barrier function, as demonstrated by elevated TEWL, and Staphylococcus aureus colonization in a sample of 30 participants with atopic dermatitis and 10 participants with healthy skin. Atopic dermatitis participants positive for S. aureus had significantly higher TEWL (i.e. impaired skin barrier) compared to atopic dermatitis participants not colonized with S. aureus ($p < .05$). Shin et al. (2011) analyzed the relationship between impaired skin integrity and S. aureus colonization in a sample of 33 healthy volunteers divided into S. aureus negative or positive groups according to baseline testing of facial skin. The positive group had greater visible skin scaling in comparison to the negative group, as well as higher levels of TEWL and pH, both signs of impaired barrier function; however, only pH was significantly different ($t$ test, $p < .01$). The Jinnestål et al. and Shin et al. studies suggested a relationship between impaired skin barrier function and S. aureus colonization, although these studies did not pinpoint whether impaired skin barrier function precedes S. aureus proliferation or vice versa.
Duckney et al. (2013) found impaired skin barrier function was an antecedent to the pathogenic proliferation of microorganisms by using a laboratory model of human epidermis to compare growth and toxicity of *S. aureus*, *S. epidermidis*, and *P. acnes* on intact versus damaged skin. *S. aureus* caused significantly greater damage to epidermal cells when applied to damaged skin compared to intact skin (*p* < .05). *S. epidermidis* and *P. acnes* also demonstrated greater proliferation when applied to damaged skin versus intact skin; however, the differences were not statistically significant. Results from a prospective observational study conducted by Larsen et al. (1998) echoed the results of laboratory studies. Larsen et al. (1998) found statistically greater numbers of pathogenic bacteria, such as *S. aureus*, on the hands of nurses with damaged skin compared to nurses with intact skin (*p* < .03). Singh, Marples and Kligman (1971) found that *S. aureus* proliferated more abundantly on damaged skin occluded with a dressing compared to damaged skin left open to the air.

Skin infection is a major clinical issue in immunocompromised patients. Wolfson et al. (1985) conducted a retrospective review of cutaneous infections in 31 patients receiving immunosuppressive therapy and found that 19% of skin infections disseminated to other sites via the bloodstream. Fungi and bacteria were implicated in 54% and 35% of infections respectively, and mortality attributed to skin infection was 16%. Adhesive tape was a common source of skin injury. Nucci and Anaissie (2002) conducted a retrospective review of 259 cases of cutaneous *Fusariosis* species infection and found that skin breakdown preceded infection in 12% of immunocompromised patients (*N* = 232). The authors noted pre-existing skin trauma data may have been incomplete due to the retrospective nature of the study. Cutaneous immune cells play a major role in preventing infection in the context of skin damage (Kupper & Fuhlbrigge, 2004); however, epidermal dendritic cell levels are well below normal following allogeneic HSCT and
may take approximately 6 months to become fully functional (Murphy, Merot, Tong Smith, & Mihm, 1985; Walsh, Athanasas-Platsis, & Savage, 1996). The incidence of CVAD-related infection in allogeneic HSCT recipients may be impacted by these factors. Given that CASI may contribute to CVAD-related infection it is important to conduct studies that will generate knowledge regarding the relationship between CASI and CVAD-related infection in the allogeneic HSCT population.

2.3.2 CVAD-Related Infection

2.3.2.1 CVAD-Related Local Infection (CRLI)

CRLI is relevant to CASI research because the signs and symptoms of local infection are included as part of the CASI syndrome (Broadhurst & Tardiff, 2016). In addition, CRLI may be a precursor to CRBSI, although this theory is controversial. Empirical evidence regarding CRLI in adult allogeneic HSCT recipients is sparse, and it is challenging to compare results between studies due to variations in CRLI definition, reporting format, and CVAD types. Petrosino et al. (1988) reported CRLI rates of 24% and 3.5% at two different time points in a prospective study that included 52 adult oncology patients and allogeneic HSCT recipients, whereas Chambers et al. (2005) found CRLI rates of 5% and 26% in a chlorhexidine dressing group and standard dressing group respectively in a similar study sample. In a prospective study of 98 pediatric and adult allogeneic HSCT recipients, 13.5% of 377 exit site skin cultures met the study criteria for local infection (Shivnan et al., 1991). Based on these studies, CRLI incidence appears to be somewhat common in adult allogeneic HSCT recipients.

2.3.2.2 CVAD-Related Bloodstream Infection (CRBSI)

CRBSI incidence densities ranging from 2.03 to 2.64 per 1,000 catheter days were found in a large retrospective study of 432 participants that included 203 (47%) allogeneic HSCT
recipients (Keeler et al., 2015). Dix et al. (2012) reported a CRBSI incidence density rate of 7.6 per 1,000 catheter days in a sample that included 41 (48.8%) adult allogeneic HSCT recipients. CRBSI incidence for allogeneic HSCT recipients was not reported separately in either of these studies. Of note, only 2.3% of participants had a T-CVAD in the Dix et al. study, whereas all participants had T-CVADs in the Keeler et al. (2015) study. This represents an important distinction as infection risk varies between non-tunneled and tunneled CVADs (Maki, Kluger, & Crnich, 2006). To my knowledge, CRBSI incidence and prevalence have not been published for outpatient adult allogeneic HSCT recipients with embedded T-CVADs.

### 2.3.2.3 CRBSI Risk Factors Relevant to Outpatient Allogeneic HSCT Recipients

CRBSI risk factors identified in previous studies are relevant to allogeneic HSCT recipients. Howell et al. (1995) assessed 15 different risk factors for CRBSI in adult oncology patients with T-CVADs, and found that neutropenia was the only independent risk factor for infection related to long-term T-CVADs. A study conducted by Møller, Borregaard, Tvede, and Adamsen (2005) supports Howell et al.’s finding. This finding is relevant for outpatient HSCT recipients because, although the majority will have an ANC $\geq 0.5 \times 10^9/L$ upon discharge to the HSCT outpatient clinic, it is possible some may not. In addition, some HSCT recipients receiving care in the outpatient setting may develop transient neutropenia. Another relevant factor for allogeneic HSCT recipients, not addressed by Howell et al. or Møller et al., is CVAD duration. CVADs in place greater than 7 days are associated with a higher risk of CRBSI, with the risk increasing as duration increases (Moro et al., 1994; Raad, et al., 1993; Safdar et al., 2002). CVAD duration in outpatient adult allogeneic HSCT recipients can vary considerably, an important element to consider when designing and interpreting studies that include CRBSI as an
outcome in this population. CVAD duration at time of enrollment is an important variable to capture at baseline when assessing CRBSI risk.

Study results regarding exit site colonization and CRLI as risk factors for CRBSI have been inconsistent. Snydman et al. (1982) compared exit site skin cultures with CVAD catheter segment cultures in 54 patients receiving total parenteral nutrition (TPN). There was concordance between at least one exit site organism and one catheter organism in all cases with positive catheter segment cultures (14 cases). In addition, fever of unknown source and exit site inflammation (i.e. CRLI) were significantly greater in the skin-culture-positive group in comparison to the skin-culture-negative group, \( p < .01 \) and \( p < .001 \) respectively. Bjornson et al. (1982) also compared catheter segment colonization to exit site colonization in patients receiving TPN. In this study 19 catheter segments tested positive with concordant positive skin culture found in 68% of these cases; however, a limitation of both the Snydman et al. and Bjornson et al. studies is that blood cultures were not analyzed by highly specific and sensitive methods such as DTP or PQBC at the time of the catheter-segment culture; therefore, neither study conclusively determined an association between positive exit site cultures and CRBSI (Safdar, Fine, & Maki, 2005).

In contrast, Olson et al. (2004) did not find concordance with respect to microorganisms identified in exit site cultures, blood cultures, and catheter segment cultures using highly specific pulsed field gel electrophoresis analysis. Although the sample was small in the Olson study (\( N = 78 \)), the findings are consistent with results reported by Raad et al. (1993) and Liñares et al. (1985) who found that intraluminal microorganisms played a greater role in CRBSI than skin flora at the exit site in CVADs in place for greater than 7 days. As CASI may increase microbial colonization and possibly CLRI at the exit site (Duckney et al., 2013; Jinnestål et al., 2014;
Larsen et al., 1998), it is possible CASI may be a risk factor for CRBSI originating from the exit site; however, no studies have evaluated the relationship between these two variables.

### 2.3.3 Strategies to Decrease CASI

Two prospective clinical studies have been conducted with the aim of decreasing CASI. Rasero et al. (2000) compared CASI between groups that included both allogeneic and autologous HSCT recipients. Two cohorts were created according to CVAD type (non-tunneled or tunneled). Participants with T-CVADs were randomized to 5-day or 10-day dressing change intervals, and those with non-tunneled CVADs to 2-day or 5-day intervals. Results were somewhat contradictory. The incidence of CASI in the 5-day groups was 14% for T-CVADs and 34% for non-tunneled CVADs; however, this difference was not tested statistically or discussed. Proportions of participants with CASI were significantly lower in the 2-day group compared to the 5-day group in the non-tunneled cohort ($p = .002$); equivalent proportions of participants with CASI occurred between the 5-day and 10-day groups in the T-CVAD cohort. The lowest incidence of CASI overall (13%) was found in the 10-day group. The results are difficult to interpret because 30 participants with T-CVADs and 52 participants with non-tunneled CVADs were withdrawn from the study due to skin toxicity, with lack of clarity about their inclusion in the final analysis. In addition, the issue of power was not addressed.

Benhamou et al. (2002) also evaluated a longer dressing change interval (15 days) compared with a shorter interval (4 days), as a means to decrease CASI in 113 pediatric HSCT recipients. Participants in the 4-day group were found to have a 3.4 fold risk of developing skin toxicity $\geq 2$ (as per Table 2.3) in comparison to participants in the 15-day group. The Benhamou et al. study is methodologically stronger than the Rasero et al. (2000) study. Benhamou et al. used intent-to-treat, and described the age of study participants and the methods of determining
the sample size. Given this study found decreased CASI with less dressing change exposure, it is possible no-dressing may be even more efficacious.

2.3.4 Studies Comparing Dressing to No-Dressing of T-CVAD Exit Sites

No-Dressing is likely to reduce the risk of CASI because it eliminates key factors that contribute to CASI, namely dressing adhesive, antiseptic solution, and cumulative dressing change exposure; however, CRBSI must also be considered when weighing the potential benefits of no-dressing against the risks. Although published studies evaluating no-dressing as a means to prevent or reduce CASI could not be located, a small number of studies were identified that compared dressing to no-dressing with respect to CVAD-related infection. Evidence is limited; however, CRBSI does not appear to be increased with no-dressing in adults with T-CVADs.

Olson et al. (2004) and Keeler et al. (2015) compared CRBSI between dressing and no-dressing groups and found statistically equivalent rates. Although study designs and sample sizes varied, both studies included allogeneic HSCT recipients and all had T-CVADs. Olson et al. conducted a prospective RCT whereas Keeler et al. used a retrospective post-test only control group design. Participants in the Olson et al. study were assigned to either dressing or no-dressing. Keeler et al. created three groups: (1) TSM dressing, (2) gauze dressing, and (3) no-dressing. Sample size in the Olson et al. study was calculated to detect a 12.5% difference with an alpha of .05 and beta of .8; however, the total number enrolled was only 78 of the required 116 due to premature closure of enrollment for non-study reasons. Although power was not addressed by Keeler et al., the sample size in that study was large ($N = 432$).

Despite differences in design and quality, the results of these studies were consistent. In the Olson et al. (2004) study, the CRBSI rate was slightly higher in the dressing group than no-dressing group, although the difference was not statistically significant ($\chi^2 = 1.84, df = 1, p =$
Time to onset of CRBSI was significantly longer in the no-dressing group by Kaplan-Meier analysis ($p = .024$). The authors acknowledged the results were limited by inadequate power. Keeler et al. (2015) found the CRBSI rate was not significantly different between the three study groups ($H = 2.632, df = 2, p = .268$). Unlike Olson et al., they reported no difference in time to CRBSI ($H = 3.761, df = 2, p = .152$). The results of these two studies are consistent with evidence regarding CRBSI pathophysiology that has shown the exit site is not the primary source of bloodstream infection in long-term T-CVADs (Liñares et al., 1985; Mermel et al., 2009; Raad et al., 1993; Safdar & Maki, 2004; Sitges-Serra & Girvent, 1999); however, CRBSI should be included as a secondary endpoint in studies evaluating the effectiveness of no-dressing in decreasing CASI given the serious consequences of CRBSI and lack of knowledge regarding the relationship between CASI and CRBSI.

Nagai et al. (2012) compared CRBSI in adult patients with pulmonary hypertension and found that the CRBSI rate was higher in the dressing group versus the no-dressing group. Lawrence et al. (2014) published findings of a quality improvement initiative in which the no-dressing approach was adopted as standard practice in adult hemodialysis patients. A bloodstream infection incidence density of 0.0786 per 1,000 catheter days was found for the no-dressing group compared to 0.153 per 1,000 catheter days for the dressing group. Like the outpatient adult allogeneic HSCT population, the patients included in the Nagai et al. study and the Lawrence et al. report had long-term T-CVADs and complex medical issues.

While the findings of individual dressing versus no-dressing studies are limited by inadequate power and/or retrospective non-randomized designs, there is a consistent pattern of equivalent CRBSI rates. A formal meta-analysis has not been conducted to compare CRBSI rates between dressing and no-dressing groups; however, evidence to date suggests no-dressing
is a safe method of decreasing CASI in outpatient allogeneic HSCT recipients with long-term embedded T-CVADs. An adequately powered RCT would be important to compare both CASI and CRBSI between dressing and no-dressing groups and to determine the efficacy and safety of no-dressing, but feasibility of such a study is an important consideration.

2.4 Summary

CASI is a common clinical problem in adult allogeneic HSCT recipients with potentially serious consequences. Evidence regarding skin barrier function in general suggests CASI may play a role in CRBSI, although this aspect of CRBSI pathogenesis has not been studied. CASI causes discomfort for patients and increased use of health care resources. Large-scale prospective studies to determine CASI incidence and prevalence are needed. Evidence suggests the outpatient adult allogeneic HSCT population may be at relatively greater risk of CASI, possibly due to high cumulative dressing exposure, effects of the preparative regimen, GVHD, and/or immunosuppressive therapy. No-Dressing may be an effective strategy to decrease CASI, but no studies have been conducted to test this hypothesis, despite evidence demonstrating that dressings and antiseptics are associated with skin irritation and damage. No-Dressing appears to be comparable to dressing with respect to CRBSI rate based on a small body of evidence, but an adequately powered RCT is needed to test this theory. A pilot study comparing CASI and CRBSI between dressing and no-dressing in adult outpatient HSCT recipients was conducted prior to designing and conducting a full-scale RCT. The methods of the pilot study are described in the next chapter.
Chapter 3: Methods

3.1 Introduction

An evaluation of the literature demonstrated the need for a pilot study comparing CASI and CRBSI in adult allogeneic HSCT recipients. The purpose of the pilot study was to determine the feasibility of implementing and completing a large-scale longitudinal RCT comparing CASI and CRBSI between dressing and no-dressing groups in the adult outpatient allogeneic HSCT population. The study was restricted to adult allogenic HSCT recipients receiving post-HSCT care in an outpatient setting because this group of patients may be particularly vulnerable to CASI. In addition, this patient group is well-suited for the no-dressing intervention given that embedding of the T-CVAD exit site has typically occurred by the time outpatient follow-up commences post-transplant. In this chapter, the study design, methods, procedures, and analysis plan are described.

3.2 Research Design

The pilot study used a prospective longitudinal RCT design. The initial aim was to enroll 26 adult allogeneic HSCT recipients receiving post-transplant care at the outpatient HSCT clinic at Vancouver General Hospital (VGH). Eligible participants were assigned to either a standard dressing group or a no-dressing group using stratified permuted block randomization. CASI was assessed weekly for 6 weeks. Participants were given a gift card of $25.00 as a token of appreciation.

3.3 Research Questions and Hypotheses

The research questions and associated hypotheses are reviewed below.
Primary Research Question:

Will there be fewer CASI episodes for the no-dressing group than the dressing group?

Hₐ: There will be significantly fewer CASI episodes for the no-dressing group in comparison to the dressing group.

Secondary Research Questions:

Secondary question 1:

Will there be a relationship between type of exit site care (dressing or no-dressing) and CASI ECOG grade > 2?

Hₐ: There will be a significant relationship between type of exit site care and CASI ECOG grade > 2.

Secondary question 2:

Will there be more CASI episodes at the last study visit than at baseline for the dressing group?

Hₐ: There will be significantly more CASI episodes at the last visit in comparison to baseline for the dressing group.

Secondary question 3:

Will there be a relationship between type of exit site care (dressing or no-dressing) and CRBSI?

H₀: There will not be a significant relationship between type of exit site care and CRBSI.

3.4 Study Objectives

The study objectives are reviewed below.

1. Evaluate the following enrollment characteristics: (1) enrollment rate, (2) time to complete enrollment, and (3) reasons for non-enrollment.

2. Evaluate the following aspects of CASI data quality: (1) CASI assessment completion rate, (2) reasons for non-completion, and (3) CASI assessment consistency.
3. Evaluate the following aspects of data quality in general: (1) data error rate, (2) missing data rate, (3) type of missing data, and (4) reason(s) for missing data.

4. Evaluate the following participant withdrawal characteristics: (1) withdrawal rate, and (2) reasons for withdrawal.

5. Obtain feedback from participants regarding their compliance with study procedures.

6. Obtain feedback from participants regarding their study experience.

7. Describe and compare baseline participant characteristics in the two study groups to determine the effectiveness of the randomization procedure in balancing the groups.

8. Calculate frequencies of dressing regimen characteristics, CRBSI incidence density, CASI grades, and rate of participant preference for no-dressing post-study to: (1) identify problems with data collection, and (2) generate preliminary information for future study planning.

9. Conduct statistical testing of the study hypotheses to: (1) identify problems with data collection, outcome measures, and statistical testing methods; and (2) generate estimates of significance, effect size, and variability for future study planning.

3.5 Setting

The pilot RCT study was conducted at the outpatient HSCT unit at VGH in British Columbia, Canada. Approximately 85 allogeneic HSCTs are performed at VGH annually. Post-transplant follow-up at the outpatient HSCT clinic begins once a recipient has achieved neutrophil engraftment, is in stable condition, and has been discharged from the inpatient setting. Recipients are assessed in the outpatient HSCT clinic every 1 to 7 days depending on health status for approximately 3 to 4 months post-HSCT. CVADs are inserted prior to HSCT using the Seldinger technique under maximal sterile barrier conditions. Outpatient HSCT clinic nurses are certified to perform CVAD care according to institutional guidelines (VCHA, 2017).
The standard practice at the study site is to maintain a dressing on the T-CVAD exit site from the time of insertion until the time of removal.

### 3.6 Sampling Plan

The goal was to enroll a total of 26 participants using a consecutive sampling approach. All allogeneic HSCT recipients transitioning to the outpatient HSCT unit following their transplant were invited to participate in the study. Enrollment was projected to take 16 weeks to complete based on the annual number of allogeneic HSCTs performed at VGH each year (85), with an expected eligibility rate of 90% (Benhamou et al., 2002), and a refusal rate of 20% (Shivnan et al., 1991).

#### 3.6.1 Sample Size Justification

There is no standard method for estimating sample sizes for feasibility and pilot studies (Cocks & Torgerson, 2013). Julious (2005) demonstrated that gains regarding decreased variance, increased precision about the mean, and increased precision of variance, diminish considerably with sample sizes \( \geq 12 \) per group. See Figure 3.1 for graphic representation of gains in precision in relation to sample size. As per recommendations made by Julious, I decided to enroll 24 participants in total (12 per group). To account for the possibility of premature participant withdrawal, my original plan included the recruitment of two additional participants (i.e. 26 participants in total).
3.7 Ethical Considerations

Regulatory ethics board (REB) approval was obtained prior to the start of enrollment. Prospective participants were given up to 7 days to read the consent form (see Appendix A) and have their questions answered. Written informed consent was required, and all study eligibility criteria had to be met for study participation. To protect participant identity, a unique study code was used to identify data recorded for study purposes. Study computer(s) and paper documents were kept in a locked office when not in use.

3.7.1 Invitation to Participate, Consent and Screening

Allogeneic HSCT recipients commencing post-transplant follow-up at the Leukemia/BMT Program of BC outpatient HSCT clinic were presented with a Letter of Invitation to Participate (LIP) (Appendix B) at their first post-transplant clinic visit. If an individual did not understand spoken or written English, arrangements were made for a professional medical translator to verbally translate the LIP. A confidential Screening Log
(Appendix C) was used to keep track of patients who received the LIP. No patient identifiers were entered in the Screening Log. Within 2 weeks of receiving the LIP, I contacted patients to offer a copy of the full consent form. I reviewed medical terminology used in the consent form prior to leaving the consent form with an individual. If after reading the consent form and having had all questions answered, an individual indicated he/she would like to participate in the study, I asked the prospective participant to describe the study in his/her own words to ensure adequate understanding. If a prospective participant did not understand spoken or written English, arrangements were made for a professional medical translator to verbally translate the definitions of medical terminology and the consent form. Reason(s) for lack of consent, if known, were entered in the Screening Log.

3.7.2 Eligibility Criteria

Eligibility criteria were designed to ensure a homogeneous sample and to ensure the safety of participants. Individuals who provided informed consent were enrolled if the following criteria were present: 19 years of age or over; recipient of an allogeneic HSCT (sibling, haploidentical, or unrelated donor) within the past 35-60 days; receiving post-HSCT follow-up care at the VGH outpatient HSCT clinic; evidence of an indwelling tunneled CVAD with cuff (either Hickman™, Leonard™ or Broviac™) inserted > 40 days prior to screening visit; embedded T-CVAD exit site as defined in the glossary; neutrophil engraftment as defined in the glossary; absence of temperature ≥ to 38° Celsius in the past 7 days; absence of infection requiring systemic IV therapy within the last 7 days; absence of abdominal abscess or endocarditis during HSCT admission and during post-HSCT outpatient follow-up; absence of active discharge and/or bleeding from the T-CVAD exit site; absence of severe CASI (i.e. > grade 3 as per the Modified ECOG Skin Toxicity Scale).
3.8 Randomization

Sequential stratified permuted block randomization was used to assign eligible participants to either the dressing or no-dressing group. Participants were stratified according to whether or not they received busulfan in the preparative regimen prior to HSCT, as this is the only factor that was shown to increase the risk of CASI in a clinical trial of HSCT recipients (Benhamou et al., 2002). Stratification was utilized to decrease Type 1 error and improve power by increasing the probability that study groups would be balanced with respect to busulfan (Kernan, Viscoli, Makuch, Brass, & Horwitz, 1999). A priori stratification of known or likely risk factors is preferable to remedial statistical strategies to address group imbalances based on post-hoc testing of baseline group homogeneity (Senn, 1994). Each stratum was composed of six permuted blocks of four. A block size of four was chosen due to the small sample size.

A randomization list for each block in each stratum was generated using sealedenvelope.com (Sealed Envelope Ltd, 2017). A graduate nursing student not associated with the study prepared the randomization lists and concealed each sequential group assignment by stratum in a sealed envelope. Each envelope was labeled with the stratum title and the number that corresponded to the order of the group assignment according to its sequence with respect to the block lists. The investigators and clinic staff were blinded to the lists.

3.9 Interventions and Materials

In this pilot RCT study the dressing group was compared to the no-dressing group with respect to CASI episodes, CASI severity, and CRBSI rate in outpatient adult allogeneic HSCT recipients. The primary independent variable was T-CVAD exit site care (i.e. dressing or no-dressing), and the primary dependent variable was CASI. As noted above, busulfan exposure was identified as an important secondary independent variable with respect to CASI (Benhamou
et al., 2002), and CRBSI was identified as an important secondary dependent variable (Olson, et al., 2004; Keeler et al., 2015).

3.9.1 Operational Definitions of Variables

3.9.1.1 T-CVAD Exit Site Care

T-CVAD exit site care was defined as a method of maintaining the health of the exit site, which may or may not involve the use of a dressing. Dressing was defined as the practice of maintaining a dressing on the T-CVAD exit site at all times, including during showering, except during dressing change. No-Dressing was defined as leaving the T-CVAD exit site open to the air, including during showering.

3.9.1.2 Busulfan Exposure

Busulfan exposure was defined as the receipt of any amount of busulfan during the HSCT preparative regimen. No distinction was made regarding low-dose or high-dose busulfan, or route of administration.

3.9.1.3 CASI

CASI was defined as the presence of one or more of the following signs and symptoms within 7 cm of the CVAD exit site (i.e. the CASI boundary area [CBA])²: erythema, edema, shiny skin, macular or papular lesions, maceration, folliculitis, induration, pruritus, discomfort (pain), discharge, vesicle(s), bulla(e), skin tear(s), exfoliation, ulceration, and/or suspected or microbiologically confirmed CRLI (Broadhurst & Tardiff, 2016). Skin abnormalities outside of

2 Broadhurst and Tardiff (2016) proposed a CBA radius of 5 cm from the CVAD exit site; however, in this study the CBA was increased to 7 cm in the operational definition of CASI because tape used to cover the dressing in the shower extends to a 7 cm radius from the exit site.
the CBA were not categorized as CASI. For participants in the dressing group, the CASI assessment was conducted 15 minutes after the exit site cleaning\(^3\).

### 3.9.1.4 CRBSI

CRBSI was defined a priori, as a BSI linked specifically to the T-CVAD by **differential time to positivity** (DTP). DTP involves the collection of two separate blood specimens for microbiological culture at the onset of fever, one from a peripheral site and one from the CVAD. According to Safdar et al. (2005), specimens should be obtained no more than 10 minutes apart. CRBSI is confirmed when cultures from both the CVAD and peripheral site are positive, with the CVAD culture turning positive \(\geq 2\) hours earlier than the peripheral culture. As per Safdar et al., neither positive CVAD tip culture, nor clinical symptoms should be used to confirm CRBSI. DTP was chosen to confirm CRBSI because this method is more likely to identify true cases of CRBSI due to its high level of specificity and sensitivity. In addition, it is standard practice at the study site to collect peripheral and T-CVAD blood cultures at the onset of fever, and to record the time of positivity. Other less precise methods may overestimate the rate of CRBSI (O’Grady et al., 2011; Safdar et al., 2005). CRBSI was reported as an incidence density calculated as recommended by Maki et al. (2006) using the following equation:

\[
\text{Number of infections} \times 1000
\]

### 3.9.2 The Dressing Intervention (Control Intervention)

It is standard practice at the VGH outpatient HSCT clinic to maintain a dressing on a T-CVAD exit site from insertion until removal. The dressing change procedure followed in the

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\(^3\) Broadhurst and Tardiff (2016) proposed that CASI assessment occur 30 minutes after antiseptic application; however, in this study a time period of 15 minutes was chosen to match standard practice at the study site.
pilot study was derived from the Policies and Procedures document for the Vancouver Coastal Health Authority (VCH-T-1500) (VCHA, 2017). For consistency, dressings were changed by certified outpatient HSCT nurses who receive training and certification regarding all aspects of dressing removal, exit site cleaning, and dressing application. The decision-making algorithm followed in the study to determine type of dressing and cleaning solution to use was the same as standard practice. See Appendix D for this algorithm. In terms of dressing application and removal, the procedures followed in the study were derived from the manufacturers’ guidelines. See Appendix E for a summary of these procedures.

Aseptic sterile technique was used to clean the CVAD exit site and external portion of the CVAD covered by the dressing (VCHA, 2017). As per standard practice at the study site, the exit site was cleaned with a single use 2 cm by 2 cm gauze sponge impregnated with antiseptic chosen according to the algorithm in Appendix D. The external CVAD was then cleaned with a second single use 2 cm by 2 cm gauze sponge impregnated with cleaning solution as per Appendix D. Following the cleaning of the external catheter, an area within a 5 cm radius of the exit site was cleaned using two single-use swab sticks impregnated with cleaning solution according to Appendix D (1.6 mL dose per swab). Skin contact with the cleaning solution was 30 seconds (i.e. 15 seconds per swab). Swabs were moved in multiple directions with friction. The area was left to air dry for a minimum of 15 minutes prior to application of the new dressing. Before the new dressing was applied, NO STING SKIN PREPTM was applied on the skin where dressing adhesive would be in contact. NO STING SKIN PREPTM is a skin barrier

4 The 15 minute drying time is standard practice on the Leukemia/BMT Outpatient Unit; however, this is a longer drying time than specified in VCH-T-1500 (VCH, 2017).
solution containing hexamethyldisiloxane and acrylate copolymer manufactured by Smith & Nephew.

Procedures regarding care of the T-CVAD with respect to personal hygiene are not specified in VCH (2017); however, the following approach is considered standard practice at the VGH HSCT outpatient clinic and was adopted for participants in the dressing group. Showering was permitted as long as precautions were taken to keep the dressing area and external portion of the CVAD dry. Participants in the dressing group were instructed to cover the dressing and external portion of the T-CVAD with waterproof material and to seal the edges with waterproof tape prior to showering. The waterproof cover was to be removed after showering, and the dressing was to be inspected for signs of dampness. If water contamination of the dressing occurred, the participant was instructed to have the dressing changed as soon as possible. A pictorial representation of the showering instructions entitled **Participant Instructions (Dressing Group)** can be found in Appendix F.

### 3.9.3 The No-Dressing Intervention (Experimental Intervention)

Participants in the no-dressing group were instructed to keep the T-CVAD exit site uncovered (i.e. without a dressing) at all times, including during showering. The CBA was to be kept out of the path of the water stream during showering, except when rinsing the exit site area after cleaning. No-Dressing participants were asked to adhere to the following T-CVAD exit site cleaning instructions: (1) a work surface was to be cleaned using a CAVI™ wipe; (2) hands were to be washed for 30 seconds using CeraVe Hydrating Cleanser™ for normal to dry skin; (3) a clean hand towel was to be placed on the work surface; (4) three packages of sterile gauze sponges (two sponges sized 2 cm by 2 cm, and one sized 4 cm by 4 cm) were to be opened and placed on the work surface; (5) the CVAD was then to be unsecured (i.e. tabs detached from the
bulldog clamps); (6) the shower was then to be entered and CeraVe Hydrating Cleanser™ placed within reach; (7) one pump of the cleanser was to be applied to the thumb and index finger; (8) the skin around the catheter exit site was to be cleaned by rubbing the cleanser back and forth in multiple directions around the exit site up to a radius of 7 cm from the exit site for 30 seconds; (9) the exit site area was then to be rinsed in the shower stream for 15 seconds. Once the shower was finished: (1) hands were to be dried with the clean hand towel; (2) the exit site area was to be dried using one sterile 2 cm by 2 cm gauze sponge, starting at the exit site and then patting dry in an expanding circular direction to a distance of a 7 cm radius from the exit site; (3) the external portion of the catheter was to be dried with the second sterile 2 cm by 2 cm gauze sponge, starting at the exit site and moving along the catheter to the point where the catheter separates into different lumens; (4) the connection points and hubs were to be dried with a sterile 4 cm by 4 cm gauze sponge. The participants were permitted to adapt these instructions for use during a sponge bath. These instructions were derived from information provided by Lawrence et al. (2014), Olson (personal communication, 2016), and the Nurse Educator for the HSCT Program at Princess Margaret Cancer Centre (Incekol, personal communication, 2016). A pictorial representation of these instructions entitled Participant Instructions (No-Dressing Group) can be found in Appendix G.

3.9.4 Procedures Applicable to Both Study Groups

In order to ensure consistency between study groups, the following aspects of T-CVAD care were the same for both study groups: (1) procedure and frequency of changing of NDs; (2) method of securement; (3) soap used during showering; (4) guidelines regarding frequency and length of showering; and (5) guidelines regarding clean clothing. These procedures are described in more detail below.
3.9.4.1 Changing of NDs and Access of the T-CVAD

The changing of catheter NDs, flushing of the NDs, and attaching of IV lines was performed by certified HSCT nurses according to VCHA (2017). The Carefusion™ ND was used and was changed every 6 to 8 days. In order to change the ND, the ND-CVAD connection point was cleaned with a single-use 70% isopropyl alcohol swab for 15 seconds and allowed to air dry for 30 seconds. A no-touch technique was used to remove the old ND and attach the new ND. Once the new ND was in place, the lumen was flushed with 20 mL sterile normal saline and 3 mL heparin solution 100 units/mL. Prior to access of the ND for blood drawing, flushing or attaching an IV line, a single-use 70% alcohol swab was used to clean the ND access surface for 15 seconds. The surface was dried for 30 seconds prior to access.

3.9.4.2 Method of Securement

Participants were asked to secure their T-CVAD in the following manner. A piece of pink waterproof tape 2.5 cm wide by 7 cm long was to be wrapped around each CVAD lumen just distal to the white plastic portion of the hub, to form a tab. Two bull dog clamps were to be used to attach the tabs to a standard hospital issued fabric necklace. The necklace was to be replaced every 7 to 8 days.

3.9.4.3 Personal Hygiene

Participants were asked to shower every 1 to 3 days, and to limit showers to 25 minutes or less. If a participant was unable to take a shower, a sponge bath was allowed instead. The exit site area was to be kept out of the direct path of the water stream during showering, except when cleaning the exit site. CeraVe Hydrating Cleanser™ for normal to dry skin was to be used for personal hygiene for participants in both study groups, and was provided at no cost. This cleanser is fragrance free and has a pH in the same range as skin. Participants were instructed to
wash their hands, with soap or cleanser and water, for 30 seconds prior to touching the external portion of the CVAD (von Eiff, Becker, Machka, Stammer, & Peters, 2001). Anti-microbial hand sanitizers were allowed if soap and/or cleanser and water not available. Participants were asked to wear freshly laundered clothes each day.

3.10 Measurement of Outcomes

3.10.1 CASI Measurement

A modified version of the ECOG Skin Toxicity Scale (1997) was used to identify and measure CASI (Benhamou et al., 2002; Broadhurst & Tardiff, 2016; Rasero et al., 2000; Silveira et al., 2010). The Modified ECOG Skin Toxicity Scale is shown in Table 3.1.

Table 3.1 Modified ECOG Skin Toxicity Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Scattered$^1$ macular eruption, or scattered papular eruption, or asymptomatic erythema$^2$, or scattered pruritus</td>
</tr>
<tr>
<td>2</td>
<td>Scattered macular eruption with pruritus or scattered papular eruption with pruritus, or erythema with pruritus, or scattered vesicular eruption, or scattered folliculitis, or scattered induration, or maceration, or generalized pruritus, or shiny skin</td>
</tr>
<tr>
<td>3</td>
<td>Generalized$^3$ macular eruption, or generalized papular eruption, or generalized vesicular eruption, or generalized folliculitis, or generalized induration (including induration along the tunnel tract), or bulla(e), or skin tear(s) &lt; 10% CBA, or pain, or discharge, or microbiologically documented CRLI</td>
</tr>
<tr>
<td>4</td>
<td>Exfoliative dermatitis, or ulcerating dermatitis, or ruptured bulla(e), or skin tear(s) ≥ 10% CBA</td>
</tr>
</tbody>
</table>

$^1$Scattered is defined as < 25% of CBA.

$^2$If a sign or symptom is not described as “scattered”, or “generalized” or a specific CBA percentage, then it can be assumed that “any area” of the sign or symptom within the CBA is intended.

$^3$Generalized is defined as ≥ 25% of CBA.

3.10.1.1 Face and Content Validity of the Modified ECOG Skin Toxicity Scale

The Modified ECOG Skin Toxicity Scale was developed by me in collaboration with my thesis committee. Construct validity of the Modified ECOG Skin Toxicity Scale was not
statistically analyzed prior to the start of the study because this process was felt to be outside of
the project scope; however, six clinical nurse experts (an HSCT nurse educator, an infusion
program educator, and four outpatient HSCT clinic nurses) reviewed the scale for face and
content validity. Methods of face and content validation described by Bannigan and Watson
(2009) and Lynn (1986) were followed. The Modified ECOG Skin Toxicity Scale was adjusted
according to feedback from reviewers.

The following is a summary of the changes and/or clarifications made to the ECOG Skin
Toxicity Scale (v. 1997). The term “scattered” was defined as “< 25% CBA”. The term
“generalized” was defined as “≥ 25% CBA”. Additional signs and symptoms were added to
grade levels as follows. Additions to grade 2 included: scattered vesicular eruption; scattered
folliculitis; scattered induration; maceration; and shiny skin. Additions to grade 3 included:
generalized vesicular eruption; generalized folliculitis; generalized induration; bulla(e); skin
tear(s) < 10% CBA; pain; discharge; and microbiologically confirmed CRLI. Additions to grade
4 included: ruptured bulla(e); and skin tear(s) ≥ 10 % CBA. It was clarified that, in situations
where skin abnormalities present within the CBA were also present elsewhere, the assessor
would decide whether the abnormality was “CASI” or part of a more generalized skin reaction
(i.e. GVHD or drug reaction) based on their clinical judgement. No changes were made to the
Modified ECOG Skin Toxicity Scale during the pilot study.

Inter-rater reliability (IRR) was not formally evaluated prior to the study; however, a
process of tandem assessment was incorporated into the study design to evaluate the consistency
of results obtained by different assessors. The goal was to complete tandem assessments for a
minimum of 20% of the total required CASI assessments. CASI assessments were conducted by
me and/or HSCT outpatient nurses who received training on the use of the Modified ECOG Skin
Toxicity Scale and the **CASI Assessment Form** (Appendix H), a study-specific form used to document CASI grade. Tandem assessments involved the independent and simultaneous assessment of the T-CVAD exit site by two trained assessors using two separate CASI Assessment Forms. In the case of a discrepancy in CASI grade, the two assessors compared their results to the Modified ECOG Skin Toxicity Scale and then adjusted the grade by consensus. The original results entered in the CASI Assessment Forms were retained so that discordant results could be identified and summarized.

### 3.10.1.2 The CASI Assessment Form

The CASI Assessment Form included the Modified ECOG Skin Toxicity Scale grading criteria and a 1:1 scale diagram of the CBA with the exit site location marked. Skin impairment was to be marked on the scale diagram using a key for CASI signs and symptoms. A set of photographs capturing different types of CASI, with identifying labels (Farris, Petty, Hamilton, Walters, & Flynn, 2015), was provided to assessors to assist in consistent identification of specific CASI signs and symptoms. CASI assessments were completed by me and a group of registered nurses working at the study site.

### 3.10.2 Measurement of CRBSI

The original plan was to confirm CRBSI using DTP as described in Section 3.9.1.4. Status of cultures (positive or negative) was determined using the BD BACTEC™ Automated Blood Culture System. In this system fluorescent technology is used to detect CO₂, which is released when microorganisms metabolize nutrients in the culture medium. Preprogrammed positivity algorithms determine if the amount of CO₂ detected signifies a positive or negative culture (BMS Diagnostics (M) SDN BHD, 2014).
3.10.3 Participant Compliance and Study Experience

At the end of the study participants were asked to complete a Participant Feedback Survey with four questions answered using a Likert scale and three open-ended questions. The questions were designed to provide an estimate of how closely participants followed the Participant Instructions regarding T-CVAD exit site care. See Appendices I and J for a copy of the Participant Feedback Survey for the dressing and no-dressing groups respectively.

3.11 Study Procedures

A summary of study procedures is located in Appendix K. Details are described below.

3.11.1 Screening Procedures

Screening procedures were completed between 35 to 60 days post-transplant in order to determine participant eligibility. The screening procedures were: (1) completion of the CASI Assessment Form; and (2) assessment to determine if the exit site suture had been removed or not; and (3) assessment to determine if the T-CVAD was embedded or not. Embedding of the cuff was confirmed if there was no movement of the cuff with very gentle movement and tugging of the external catheter (i.e. “tug test”).

3.11.2 Follow-Up Procedures

On the first study visit, the participant received the Participant Instructions document applicable to their study group, and I verbally reviewed the content with them. Participants were asked to demonstrate and/or describe the procedures after the education session. At the first visit, and all subsequent visits, the CASI Assessment Form was completed, with a variation of +/- 1 day allowed. In a few cases, a longer deviation was allowed for logistical reasons. In the dressing group, CASI assessments were completed 15 minutes after the exit site was cleaned with antiseptic solution. The time when cleaning finished and the time when the CASI
assessment was performed were entered in the CASI Assessment Form in order to capture actual timing of assessments.

3.11.3 End of Study Procedures

At the final study visit, in addition to the CASI assessment, participants were asked to complete the Participant Feedback Survey. No-Dressing participants were asked whether they wanted to continue with no-dressing or go back to having a dressing. The participant’s preferred option for post-study T-CVAD exit care was discussed with their outpatient HSCT clinic physician.

3.12 Criteria for Withdrawal from the Study

It was decided, a priori, that the occurrence of any of the following situations during the study would necessitate a participant’s early withdrawal from the study: planned T-CVAD removal or accidental egression; development of neutropenia (ANC < 0.5 x 10⁹/L) for > 7 consecutive measurements on different days; temperature of ≥ 38° Celsius at one or more time points for > 3 consecutive days; T-CVAD removal due to positive blood cultures or no longer needed; admission to hospital for a period > 14 consecutive days; participant preference to withdraw prior to study completion; and attending Leukemia/BMT physician recommendation to withdraw participant for medical reasons not listed above. If a participant was withdrawn from the study for any of these reasons, their data collected to that point were retained for the analysis.

3.13 Safety

It was anticipated that episodes of CRBSI would be uncommon based on CRBSI incidence densities reported by Keeler et al. (2015) and Dix et al. (2012) which were 2.03 and 7.6 per 1,000 catheter days respectively. The plan was to report episodes of CRBSI to the Regional Medical Director for Infection Control at VCHA from the start of enrollment until
completion of the study. In the event of a safety concern, the study was to be placed on hold or stopped depending on the nature of the event. It was planned, a priori, that participants in the no-dressing group who were hospitalized during the study would be required to have a dressing on their T-CVAD exit site from the start to the end of the admission.

3.14 Data Items

The data collection form (DCF) for the study is included in Appendix L. Data were obtained from medical charts, the CASI Assessment Forms, and the VGH Department of Microbiology BD Epicenter database.

3.14.1 Screening Data

The following data were collected to determine eligibility: date of written consent; date of screening visit; age; date of most recent allogeneic HSCT; HSCT donor type (i.e. sibling, haploidentical relative, or unrelated donor); type of HSCT preparative regimen (i.e. with busulfan or no busulfan); date of transition of care from inpatient to outpatient HSCT unit; type of CVAD; date of T-CVAD insertion; date T-CVAD exit site suture removed; status of T-CVAD exit site (i.e. embedded or not); status of discharge at T-CVAD exit site (i.e. discharge or bleeding or neither); most recent total white blood cell count (WBC); absolute neutrophil count (ANC) within 7 days of randomization; history of temperatures $\geq 38 \, ^\circ$ Celsius within past 7 days (yes/no) prior to randomization; infection requiring systemic IV therapy in the past 7 days.

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5 Defined as the first visit at the outpatient HSCT unit following the participant’s allogeneic HSCT.
6 Participants were required to have one of the following types of tunneled CVADs in order to participate: Hickman™, Leonard™, or Broviac™.
(yes/no); history of abdominal abscess (yes/no); history of endocarditis (yes/no); and CASI grade at screening visit (0, 1, 2, 3 or 4).

### 3.14.2 Additional Baseline Data

Additional baseline data were collected within 1 week of randomization: sex; disease (i.e. reason for HSCT); stem cell source (PBSCs, bone marrow, or cord blood); HLA match (10/10, 9/10, 8/10, or other); presence or absence of active GVHD (yes/no) according to NIH criteria (Jagasia et al., 2015); GVHD organ involvement at baseline (if applicable); SCST within past 7 days (yes/no); intensity of preparative regimen (RIC or myeloablative); and number of T-CVAD lumens.

### 3.14.3 Follow-Up Data

The study follow-up period spanned the date of randomization to the date of the final study visit (i.e. Week 6 Visit). The following data were collected during the follow-up period: CASI grade at each assessment time point; if CASI Assessment Form not completed, reason for non-completion; date(s) of unscheduled dressing changes; WBC and ANC result on day of each CASI assessment (+/- 2 days); date of all episodes of temperatures ≥ 38° Celsius as per the medical chart; date of blood cultures meeting the DTP criteria for CRBSI and organism(s) cultured; date of positive microbiological results for specimen(s) obtained from the T-CVAD exit site and organism(s) cultured; days of SCST; new onset of skin GVHD as per NIH Consensus Criteria (Jagasia, et al., 2015); admission and discharge dates of all hospital admissions; date of relapse and/or death (if applicable); Participant Feedback Survey completion

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7 History of abdominal abscess and history of endocarditis was defined as the occurrence of either of these events during the participant’s inpatient admission for allogeneic HSCT.
(last visit only); if Participant Feedback Survey not completed, reason for non-completion; if applicable, reason for study withdrawal; and date of final study visit. For the no-dressing group only, the participant’s choice regarding T-CVAD exit site care at end of study (i.e. continue with no-dressing or return to dressing) was documented.

3.15 Study Database

I entered study data into an excel spreadsheet. Data were identified by a unique code assigned to each participant at the time of randomization. Data cleaning was performed once data entry had been completed as per Polit (2010). Following completion of data cleaning, 100% of the clinical data was reviewed by two volunteer auditors. The auditors were registered nurses employed at the study site but not involved with the study. The auditors compared the data recorded in the DCFs to source information in the medical charts and CASI Assessment Forms.

3.16 Data Analyses

Quantitative feasibility thresholds were established a priori when appropriate to facilitate objective interpretation of the results. Feasibility thresholds have been used in other pilot studies to determine if it is reasonable to proceed with a large-scale trial (Arnold et al., 2009; Thabane et al., 2010). In a variety of pilot and feasibility studies that have been published, the feasibility thresholds used were within 5% to 20% of the projected goal (Arnold et al., 2009). With respect to testing of the hypotheses, alpha was set at .05 to provide an estimate of significance. SPSS version 25 (IBM Corp., 2017) was used for statistical analyses. Study data were imported to SPSS from the excel database after data entry, data cleaning, and auditing had been completed. It was decided a priori that a multiple-imputation model of estimating missing values would be used, if necessary, to manage missing data. Qualitative data were summarized according to relevant themes. Details of the analyses are described below.
3.16.1 Enrollment

3.16.1.1 Enrollment Rate

The enrollment rate was determined by calculating the ratio of participants enrolled to the number of allogeneic HSCT recipients presented with the LIP expressed as a percentage. The feasibility threshold was 70% because a lower enrollment rate was considered a feasibility concern.

3.16.1.2 Time to Complete Enrollment

Time to complete enrollment was defined as the number of days between the start of enrollment (i.e. date of REB approval) and the end of enrollment (i.e. date 26th participant enrolled). The feasibility threshold was set at a time period that was 25% longer than the projected period of 16 weeks (i.e. 20 weeks). Because 16 weeks was considered a generous estimate, a time period of 20 weeks or longer was considered as a significant barrier to the completion of a large-scale RCT.

3.16.1.3 Reasons for Non-Enrollment

The frequency of reasons for non-enrollment, as collected in the Screening Log, were recorded and summarized according to the following categories: (1) prospective participant refused consent form; (2) translator not available for prospective participant when necessary; (3) prospective participant self-identified a lack of eligibility upon reading consent form; (4) prospective participant declined to participate after reading consent form; (5) no consent – other reasons; (6) prospective participant consented but ineligible following screening. Qualitative data regarding reasons for refusing the consent form and declining to participate after reading the consent form were analyzed.
3.16.2 CASI Data Quality

The quality of CASI data is important given that CASI is the dependent variable for the primary hypothesis and for two of the secondary hypotheses.

3.16.2.1 CASI Assessment Completion Rate:

The CASI assessment completion rate was determined by calculating the ratio expressed as a percentage of completed CASI assessments to required CASI assessments. The feasibility threshold was set at 95%. Less than a 95% completion rate of scheduled CASI assessments was viewed as a serious feasibility issue.

3.16.2.2 Reason(s) for Non-Completion

The reasons for not completing the CASI assessment were categorized as follows: (1) error, (2) participant refused, (3) lack of nurse/researcher time, (4) lack of participant time, (5) participant absent, and (6) other. The frequencies for each reason were calculated.

3.16.2.3 CASI Assessment Consistency

3.16.2.3.1 Tandem Assessments

Consistency in CASI assessment was evaluated by completing tandem assessments for a subset of CASI assessments, and then comparing the results for concordance. The aim was to complete tandem assessments for a minimum of 20% of the total number of required CASI assessments. The ratio of actual tandem CASI assessments to planned tandem assessments was calculated and expressed as a percentage. A rate of tandem assessment completion of < 20% of the total CASI assessments was considered a feasibility issue.
3.16.2.3.2 Discordant Findings Rate for Tandem Assessments

The ratio of total discordant findings to total possible findings for tandem CASI assessment was calculated and expressed as a percentage. The feasibility threshold for discordant findings was set at 10%. A percentage > 10% of findings that were discordant was considered a feasibility issue indicating that it would be necessary to further test the Modified ECOG Skin Toxicity Scale prior to use in a future study.

3.16.3 Data Quality in General

3.16.3.1 Data Error Rate

The data audit was intended to identify discrepancies between the data collected and the source documents. The data error rate was determined by calculating the ratio of data errors to total collected data. The result was expressed as a percentage. The error threshold was set at 5%. An error rate of > 5% was considered a feasibility issue.

3.16.3.2 Missing Data Rate

The missing data rate was determined by calculating the ratio of missing data values to total expected data. The result was expressed as a percentage. The feasibility threshold was set at 10%. A missing data rate > 10% was considered to be a serious feasibility issue.

3.16.3.3 Missing Data Type

Missing data were reviewed to determine if the missing data rate was > 5% for specific data items. A missing data rate of > 5% for a specific data item was considered a feasibility issue.

3.16.3.4 Reasons for Missing Data

The reasons for missing data were noted and summarized according to the following categories: (1) error, (2) data item not available in source documents, and (3) unknown.
3.16.4 Participant Withdrawal

While early withdrawal occurs in clinical studies, a high rate of withdrawal poses a significant threat to the validity of results. The feasibility threshold for the withdrawal rate was set at > 20%. A withdrawal rate > 20% was considered a serious feasibility issue. Reasons for withdrawal as per Section 3.12 were obtained and summarized.

3.16.5 Participant-Dependent Compliance

3.16.5.1 Quantitative Survey Data Analysis

The mean scores for each question with a Likert scale response in the Participant Feedback Survey were calculated separately for each group. Higher scores indicated lower compliance with the study procedures for site care. For both groups it was determined that the following mean scores would be considered a feasibility concern: ≥ 3 for question 1; ≥ 4 for question 3; ≥ 3 for question 4; and/or ≥ 3 for question 5.

3.16.5.2 Feedback from Participants Regarding Procedure Compliance

Qualitative data derived from the Participant Feedback Survey regarding participant-dependent compliance were extracted and summarized using themes.

3.16.6 Feedback from Participants Regarding Study Experience

Qualitative data derived from the Participant Feedback Survey regarding study experience were extracted and summarized using themes.

3.16.7 Analysis of Baseline Participant Characteristics

The following continuous baseline variables were evaluated for normality by study group using the Kolmogorov-Smirnov and Shapiro-Wilk tests: CASI grade, age, days post HSCT, days post T-CVAD insertion, WBC, and ANC. Homogeneity of variance between study groups was tested for the following baseline variables prior to the testing of the hypotheses: age; sex;
regimen (busulfan or no busulfan); stem cell source (peripheral blood, bone marrow, or cord blood); GVHD status (active GVHD or no active GVHD); SCST (yes or no); donor type (sibling, haploidentical, or unrelated); HLA match (10/10, 9/10, or 8/10); disease (AML, ALL, MDS, Lymphoma, Other); days post HSCT; days post T-CVAD insertion; WBC; ANC; CASI grade; dressing type (Tegaderm Advanced Securement, Tegaderm Diamond Film, Sterile Gauze, or Other). Homogeneity of variance for T-CVAD type (Hickman™, Broviac™, or Leonard™) was not tested because all participants had triple lumen Hickman™ Lines. The Levene’s test and independent samples $t$ test were used to test for homogeneity of variance for continuous variables. The chi-square test for independence or the Fisher’s exact test was used to test categorical variables, depending on the number of categories and lowest cell count. Measures of central tendency and variance were calculated.

### 3.16.8 Frequency Analyses

The total number of dressing changes was calculated by group. The frequency of dressing types for each group were calculated according to the following categories: Mepore™ dressing, Tegaderm IV Advanced Securement™ dressing, Tegaderm Diamond Pattern Film™ dressing, plain gauze dressing, other. The frequencies of CASI episodes (any grade) for both groups combined and by group were calculated. The frequencies of CASI episodes by grade for both groups combined and by group were calculated. Mean episodes of CASI by grade were compared by group using the $t$ test for independence. The proportions of participants with one or more episodes of CASI (any grade) for both groups combined and by group were calculated using the Fisher’s exact test. The original plan was to calculate DTP-confirmed CRBSI incidence density; however, BSI incidence density was calculated instead because one set of
blood cultures were drawn only due to error. For the no-dressing group, the percentage of participants who continued with no-dressing at the end of the study was calculated.

3.16.9 Testing of Study Hypotheses

Study hypotheses were tested statistically to identify issues with data collection, outcome measures, and the statistical testing methods. Significance, effect size, and variability were generated. An intent-to-treat approach was followed. Alpha was set at .05. Due to the small sample size, p values and effect sizes are estimates, and give some conditional information for future study design, rather than being applicable to clinical decision-making.

3.16.9.1 Primary Hypothesis

Two-way ANOVA was used to test the hypothesis that mean CASI episodes would be significantly fewer with no-dressing in comparison to dressing and to adjust for the influence of busulfan exposure on CASI rates (Benhamou et al., 2002). As per Kahan and Morris (2011), it is advisable to adjust for stratification factor(s). Each CASI assessment demonstrating grade 1, 2, 3, or 4 was counted as one episode of CASI, with up to six CASI episodes possible in total per participant (not including the baseline assessment). A participant’s data were included in the analysis as long as there was a minimum of four data points out of six possible assessments. A directional outcome (i.e. significantly greater mean CASI episodes in the dressing group) was anticipated in view of studies demonstrating the damaging effect of dressings and antiseptics; however, as CASI has not been compared previously between dressing and no-dressing, a two-tailed test was used. Levene’s test of equality of error variances was used to determine if there was significant variation between the dressing and no-dressing groups (Pallant, 2013). Interaction effects between the two independent variables were analyzed, and partial eta squared
was calculated as an estimation of effect size with respect to the relationship of the independent variables to CASI (Pallant, 2013).

### 3.16.9.2 Secondary Hypotheses

The original plan was to use the chi-square test of independence to test the hypothesis that there would be a significant relationship between type of exit site care and CASI ECOG grade \( \geq 2 \); however, due to the low number of observations available for some cells, the Fisher’s exact test was used. The dependent variable categories were “CASI ECOG grade \( \geq 2 \)” and “CASI ECOG grade \(< 2\)”. Effect size was analyzed using the phi coefficient index (Polit, 2010). The McNemar’s exact test was used to test the hypothesis that there would be a significantly greater proportion of CASI episodes at the end of the study in comparison to baseline episodes for the dressing group. The dependent variable categories were “CASI” and “No CASI”. A decision was made during the analysis to compare the proportion of CASI episodes at baseline and end of study in the no-dressing group using the McNemar’s exact test. The phi coefficient index was calculated to estimate effect size for both of these analyses (Polit, 2010). With respect to the null hypothesis that there would not be a relationship between type of exit site care and CRBSI, the original plan was to use the chi-square test of independence; however, due to the low number of observations available for some cells, the Fisher’s exact test was used. Effect size was analyzed using the phi coefficient index (Polit, 2010).

### 3.16.9.3 Post-Hoc Analyses of Clinical Variables Relevant to CASI and/or CRBSI

Several variables were identified in Chapter 2 that had the potential to have a moderating impact on the hypotheses being tested: days of SCT; days of active skin GVHD; number of hospitalizations; mean ANC; days of follow-up, presence of fever (yes/no); presence of CVAD-related local infection (yes/no); relapse (yes/no); and death (yes/no). Post-Hoc analysis for
homogeneity of variance between groups was conducted to determine if these factors were balanced between the study groups. Continuous variables were evaluated using Levene’s test for equality of variances and the $t$ test for equality of means.

**3.16.10 Summary**

This pilot study tested the feasibility of conducting a large-scale longitudinal RCT comparing CASI episodes, CASI severity, and CRBSI in adult outpatient allogeneic HSCT recipients. Twenty-four participants were enrolled and were assigned to either a dressing or a no-dressing group using stratified block randomization. CASI was measured using a modified version of the ECOG Skin Toxicity Scale (v. 1997) and was assessed weekly for 6 weeks by me and a team of nurses at the study site. Elements of the study that were evaluated for feasibility included enrollment, data quality, participant withdrawal, participant compliance, and the analytical plan. Feasibility thresholds were set a priori to facilitate objective interpretation of the study results. In the next chapter the results of the pilot study are presented.
Chapter 4: Findings

4.1 Introduction

This chapter describes the study participants and the study findings. The purpose of this pilot study was to evaluate key elements of the study design to determine the feasibility of conducting a fully powered prospective longitudinal RCT comparing CASI episodes, CASI severity, and CRBSI rates between dressing and no-dressing groups in adult outpatient allogeneic HSCT recipients.

4.2 Enrollment

Enrollment for the pilot study commenced September 25, 2017 and finished July 13, 2018. A consecutive sampling method with stratified randomization was utilized as planned with accrual of 24 participants (12 per group) achieved, as recommended by Julious (2005). Of the total number enrolled, 23 participants completed all six study visits. During the study recruitment period, 80 patients underwent allogeneic HSCT at the study site. The original study plan called for a sample of 26 participants to accommodate an anticipated withdrawal rate of 20%; however, due to a slower than projected rate of enrollment, a decision was made to stop accrual at 24 participants.

4.2.1 Enrollment Rate

The enrollment rate was the ratio of the number of individuals enrolled to the number of individuals presented with the LIP. Although 80 individuals underwent allogeneic HSCT during study recruitment, 18 were not presented with the LIP. Reasons are presented in Section 4.2.3. Sixty-two patients received the LIP, with 26 consenting to participate. It was determined two of these patients were ineligible following screening; in total 24 participants were enrolled in the
study. The overall rate of enrollment was 39% which was well below the feasibility threshold of 70%; therefore, the feasibility threshold was not met.

4.2.2 Time to Complete Enrollment

Total time for enrollment was 291 days (41.6 weeks). Enrollment was projected to take 16 weeks based on an average of 85 HSCTs per year and assuming an 80% acceptance rate. The feasibility threshold was set at a time period 25% longer (i.e. 20 weeks). The time to complete enrollment was over 2 and ½ times longer than projected (i.e. 260%); therefore, the feasibility threshold was not met.

4.2.3 Reasons for Non-Enrollment

As noted above, 80 individuals were between Days 35 and 60 post allogeneic HSCT during the recruitment period. Of these individuals, 78% \( (n = 62) \) received the LIP. Reasons for 22\% \( (n = 18) \) of individuals not receiving the LIP are presented in Table 4.1.

<table>
<thead>
<tr>
<th>Reason Category</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not followed in outpatient unit between Day 35 to 60 post HSCT</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>Logistical issues (e.g. significant psychosocial issues, other)</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>CVAD type not eligible(^1)</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Translator not available</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Fever and/or IV antibiotics (ineligible)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>18</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

\(^1\)Eligible CVADs included the following tunneled lines: Hickman™, Leonard™ or Broviac™.

As noted previously, 36 individuals who received the LIP declined to participate, thus the study refusal rate was 58\%. Individuals were asked to provide their reason(s) in their own words. Seven individuals provided two reasons, and the remainder provided either one reason or no reason. The frequency each reason was cited is summarized in Table 4.2 below. “Feeling more secure with a dressing on the exit site” was the most commonly cited reason (20%).
Individuals who provided this reason were asked to elaborate. Two individuals provided additional information, which was captured in one of the more specific categories; however, seven individuals did not elaborate.

Table 4.2 Frequencies of reasons cited regarding decision not to participate

<table>
<thead>
<tr>
<th>Reasons Cited for Declining to Participate</th>
<th>N</th>
<th>% of all reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feel more secure with a dressing on the exit site</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Prefer to stay with “status quo”</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>No reason provided</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Feel overwhelmed already</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Worried about infection</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>My partner doesn’t want me to participate</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Don’t want to be responsible for no-dressing procedure</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Don’t see a benefit (exit site skin OK)</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Already participating in one or more studies</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total reasons cited</strong></td>
<td>44</td>
<td>100</td>
</tr>
</tbody>
</table>

With respect to the need for translation services, a professional medical translator assisted prospective participants with the consent process on three occasions. In two of these instances, the individual agreed to participate in the study.

4.3 CASI Data Quality

4.3.1 CASI Assessment Completion Rate

A total of 135 out of 138 CASI assessments were performed resulting in a completion rate of 98%. In this case the feasibility threshold was met as the completion rate was above 95%.

4.3.2 Reason(s) for Non-Completion

In two cases CASI assessments were not completed due to error. In these instances, the dates of participants’ clinic visits were changed for clinical reasons. I was not able to be on the unit on those dates, and I did not communicate clearly to other CASI assessors who were working on those dates that assessments needed to be done. A third CASI assessment was missed due to lack of assessor availability.
4.3.3 Tandem Assessments

The feasibility target for tandem assessments was met, with tandem assessments completed for 21% of all assessments, a finding slightly above the minimum threshold of 20%.

4.3.4 Discordant Findings Rate for Tandem Assessments

The feasibility threshold for discordant findings was not met. Discordant grading occurred for 22% of the tandem assessments which was above the feasibility threshold of 10%.

4.4 Data Quality in General

4.4.1 Data Error Rate

The feasibility threshold was met regarding overall data error rate; the error rate was < 5%. The majority of errors involved inaccurate date transcriptions. Errors identified during the audit were corrected prior to the analysis.

4.4.2 Missing Data Rate

The feasibility threshold for expected data overall was met. The missing data rate was < 5%, which was well below the threshold of 10%.

4.4.3 Missing Data Type

The feasibility threshold of < 5% missing data for specific data items was not met regarding DTP, date of T-CVAD, days post T-CVAD, type of cleaning solution, and use of NO STING SKIN PREP™. DTP was missing for the one episode of BSI that occurred because only one set of blood cultures was drawn and it was unclear whether the set collected was from a peripheral site or the T-CVAD. In this case, the participant presented to the Emergency Room and the blood samples were drawn there. Date of T-CVAD insertion was missing for two participants because this information could not be located in the medical charts. Consequently, days post T-CVAD insertion could not be calculated. CASI grade was missed due to error in
two cases and lack of CASI assessor availability in one case. Cleaning solution and use of NO STING SKIN PREP™ were missing in three cases because the CASI assessment was not done, and in the remaining cases because the assessor did not check the applicable boxes in the CASI Assessment Form. Details are shown in Table 4.3.

### Table 4.3 Frequencies of missing data types

<table>
<thead>
<tr>
<th>Data Item</th>
<th>Total Expected Observations</th>
<th>Missing n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP data</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Date of T-CVAD insertion</td>
<td>24</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Days post T-CVAD insertion</td>
<td>24</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Cleaning solution</td>
<td>72</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Use of NO STING SKIN PREP™</td>
<td>72</td>
<td>5 (7)</td>
</tr>
<tr>
<td>CASI grade</td>
<td>161</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Dressing type</td>
<td>96</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>450</strong></td>
<td><strong>20 (4)</strong></td>
</tr>
</tbody>
</table>

*Feasibility threshold not met.

1. One participant censored due to early withdrawal
2. Expected observation = 1 (based on occurrence of one BSI event during the study)
3. Expected observations = 72 (6 weekly assessments x 12 participants)
4. Expected observations = 161 (baseline assessment and 6 weekly assessments x 23 participants)
5. Expected observations = 96 (baseline assessment x 24 participants and 6 weekly assessments x 12 participants)

4.5 Participant Withdrawal

It was anticipated that 8% of participants might not complete all six study visits. The actual withdrawal rate was 4%; therefore, the feasibility threshold was met. One participant was withdrawn prior to the first weekly visit due to accidental T-CVAD egression.

4.6 Participant-Dependent Compliance

4.6.1 Quantitative Survey Data Results

Questions 1, 3, 4 and 5 of the Participant Feedback Surveys were answered using a 5-point Likert scale. The lower the number on the scale, the greater the compliance demonstrated.
The mean score for each Likert-scale question is presented by group in Tables 4.4 and 4.5. Mean scores were not compared statistically between the groups.

**Table 4.4 Mean scores for survey questions (dressing group, n = 12)**

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Did you use CeraVe Hydrating Cleanser™ when showering?</td>
<td>3.25</td>
</tr>
<tr>
<td>3. During the study I showered (i.e. frequency of showering):</td>
<td>2.42</td>
</tr>
<tr>
<td>4. How often were you able to follow the instructions regarding “keeping your dressing and central line dry during showering”?</td>
<td>1.50</td>
</tr>
<tr>
<td>5. How often do you think your dressing became damp or wet during showering?</td>
<td>3.33</td>
</tr>
<tr>
<td><strong>Mean Score (all questions)</strong></td>
<td><strong>2.63</strong></td>
</tr>
</tbody>
</table>

**Table 4.5 Mean scores for survey questions (no-dressing group, n = 8)**

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Did you use CeraVe Hydrating Cleanser™ when showering?</td>
<td>1.00</td>
</tr>
<tr>
<td>3. During the study I showered (i.e. frequency of showering):</td>
<td>2.11</td>
</tr>
<tr>
<td>4. How often were you able to follow the 4 steps regarding “how to clean the area around the exit site” when in the shower?</td>
<td>1.44</td>
</tr>
<tr>
<td>5. How often were you able to follow the 5 steps regarding what to do “once you finished your shower”?</td>
<td>1.25</td>
</tr>
<tr>
<td><strong>Mean Score (all questions)</strong></td>
<td><strong>1.45</strong></td>
</tr>
</tbody>
</table>

**4.6.2 Feedback from Participants Regarding Procedure Compliance**

The qualitative survey data provided insight into reasons for non-compliance. The following comments are from participants in the dressing group regarding CeraVe™ cleanser: “I didn’t use the CeraVe™ cleanser – it smelled bad”; Occasionally I used Allenbury's soap as it is easy on the skin”; “the CeraVe didn’t make suds...Sometimes I used a gentle baby wash” One participant in the no-dressing group stated: “I didn't use CeraVe all the time. I used water sometimes because I didn't want to use the cleaner too often.” Some participants in both groups
reported a lack of compliance with other aspects of the showering instructions. In the dressing group the following information was shared: “Never showered the top part of my body because dressing would get wet even with the bag”; “The bags provided (I felt) did not adequately cover the dressing to tape around it. I often used ziploc bags instead.” One participant in the no-dressing group stated: “I didn’t feel that I needed the sterile gauze to dry the catheter. I felt that a clean, dry washcloth would suffice.”; and another noted: “Having the tubes hang while showering causes slight discomfort so I taped them to my chest.”

4.7 Feedback from Participants Regarding Study Experience

With respect to feedback regarding study procedures in general, two participants in the dressing group stated: “It was a lot of work showering – time consuming – bagging and taping”; “The dressing was fine except for the showering part”. In contrast, one participant in the no-dressing group stated: “Showering is much easier without a dressing”. The following are comments from participants in the no-dressing group regarding their experience of not having a dressing: “Prefer no-dressing because no rash.”; “I really liked not having a dressing.”; “The most noticeable effect was the lack of itching. The dressings always itched.” Participants also provided ideas for improving the instructions. One participant in the no-dressing group stated: “The drying process is tedious and could be simplified.”; and another commented: “The only confusion in the beginning in the instruction picture was showing two small packages of gauze to use to dry the site and only one was needed.”

4.8 Analysis of Baseline Participant Characteristics

Continuous baseline variables were evaluated for normality by study group using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Age and CASI grade were normally distributed for both tests for both study groups, although the p value of the Kolmogorov-Smirnov test for the
dressing group was only marginally greater than .05 (KS, df = 12, p = 0.052). Normality for other baseline continuous variables was inconsistent between study groups and/or between tests. Days post HSCT, WBC and ANC were positively skewed, whereas days post T-CVAD insertion, a risk factor for CRBSI, had a multi-modal distribution. See Table 4.6 for details.

Table 4.6 Normality of baseline variables by study group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Kolmogorov-Smirnova</th>
<th>Shapiro-Wilk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistic df Sig.</td>
<td>Statistic df Sig.</td>
</tr>
<tr>
<td>CASI grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing</td>
<td>.241 12 .052  .205 12 .174</td>
<td>.894 12 .133  .891 12 .123</td>
</tr>
<tr>
<td>No-Dressing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing</td>
<td>.205 12 .173  .105 12 .200</td>
<td>.918 12 .269  .980 12 .269</td>
</tr>
<tr>
<td>No-Dressing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days post HSCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing</td>
<td>.237 12 .062  .256 12 .028</td>
<td>.842 12 .029  .756 12 .003</td>
</tr>
<tr>
<td>No-Dressing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days post T-CVAD insertion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-Dressing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing</td>
<td>.313 12 .002  .240 12 .055</td>
<td>.787 12 .007  .905 12 .183</td>
</tr>
<tr>
<td>No-Dressing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing</td>
<td>.289 12 .007  .244 12 .048</td>
<td>.764 12 .004  .882 12 .094</td>
</tr>
<tr>
<td>No-Dressing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aLilliefors Significance Correction

Baseline variables were tested for homogeneity of variance between study groups. The Levene’s test and independent samples t test were used for continuous variables. For categorical variables, either the chi-square test for independence or the Fisher’s exact test was used, depending on the number of categories and lowest cell count. Group homogeneity of variance was found for all baseline variables indicating the stratified randomization process was effective in balancing participant characteristics. See Table 4.7 for details.
Table 4.7 Participant characteristics at baseline by study group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dressing N=12 (50%)</th>
<th>No-Dressing N=12 (50%)</th>
<th>p value¹</th>
<th>Chi-square³</th>
<th>Fisher’s³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean (SD)</td>
<td>49.42 (16.25)</td>
<td>50.33 (11.65)</td>
<td>.88</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (21%)</td>
<td>6 (25%)</td>
<td>NA</td>
<td>.68</td>
<td>NA</td>
</tr>
<tr>
<td>Male</td>
<td>7 (29%)</td>
<td>6 (25%)</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>Regimen, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td>9 (38%)</td>
<td>10 (42%)</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>No busulfan</td>
<td>3 (12%)</td>
<td>2 (8%)</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>Stem cell source, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>11 (46%)</td>
<td>11 (46%)</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>GVHD status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active GVHD</td>
<td>0 (0%)</td>
<td>4 (17%)</td>
<td>NA</td>
<td>NA</td>
<td>.09</td>
</tr>
<tr>
<td>No active GVHD</td>
<td>12 (50%)</td>
<td>8 (33%)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>SCST, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (17%)</td>
<td>5 (21%)</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>No</td>
<td>8 (33%)</td>
<td>7 (29%)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Donor type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>5 (21%)</td>
<td>5 (21%)</td>
<td>NA</td>
<td>.58</td>
<td>NA</td>
</tr>
<tr>
<td>Haploidentical</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td>7 (29%)</td>
<td>6 (25%)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA match, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/10</td>
<td>10 (83%)</td>
<td>9 (75%)</td>
<td>N/A</td>
<td>.59</td>
<td>N/A</td>
</tr>
<tr>
<td>9/10</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/10</td>
<td>0 (0%)</td>
<td>1 (8%)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>4 (33%)</td>
<td>5 (42%)</td>
<td>NA</td>
<td>.51</td>
<td>NA</td>
</tr>
<tr>
<td>ALL</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td>3 (25%)</td>
<td>2 (17%)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2 (17%)</td>
<td>0 (0%)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (8%)</td>
<td>3 (25%)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days HSCT, Mean (SD)</td>
<td>39.25 (3.75)</td>
<td>39.08 (5.23)</td>
<td>.93</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Days T-CVAD, Mean (SD)²</td>
<td>135.00 (79.30)</td>
<td>129.50 (76.37)</td>
<td>.87</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>WBC, Mean (SD)</td>
<td>7.91 (5.71)</td>
<td>7.77 (3.63)</td>
<td>.94</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ANC, Mean (SD)</td>
<td>5.82 (5.27)</td>
<td>5.64 (3.49)</td>
<td>.93</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CASI grade (0-4), Mean (SD)</td>
<td>1.58 (.90)</td>
<td>1.33 (1.07)</td>
<td>.54</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dressing type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tegaderm Adv Sec™</td>
<td>10 (83%)</td>
<td>9 (75%)</td>
<td>NA</td>
<td>.28</td>
<td>NA</td>
</tr>
<tr>
<td>Tegaderm Diamond Film™</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile gauze</td>
<td>0 (0%)</td>
<td>1 (8%)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>2 (17%)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Equal variance not assumed; 2-tailed.
²Two observations missing in no-dressing group for Days T-CVAD (n = 10).
³Percentages for sub-group proportions rounded up; therefore, group total may not equal 100%.
4.9 Descriptive Frequency Analyses

4.9.1 Dressing Regimen Characteristics during the Study

The total number of dressing changes during the study was calculated by group. Total number of dressing changes in the no-dressing group = 0 (n = 11), and 78 (n = 12) in the dressing group. Of the 78 dressing changes in the dressing group, six were additional unscheduled dressing changes. Dressing regimen information was not collected for unscheduled dressing changes. During the 6 week study period, the most common dressing type was the Tegaderm Advanced Securement™ (81%), and the second most common was the Tegaderm Diamond Film™ (15%). No other dressing types were used. With respect to cleaning solutions, chlorhexidine 2% in isopropyl alcohol 70% was used most frequently (47%), chlorhexidine 2% only was the second most frequently used (29%), and povidone-iodine 10% was used the least frequently (15%). NO STING SKIN-PREP™ was used during most dressing changes (81%). The reasons NO STING SKIN-PREP™ was not used were not collected.

4.9.2 CASI Details

The frequency of each CASI grade during the study was summarized for combined groups and the groups separately in Tables 4.8 and 4.9 respectively. Mean episodes of CASI by grade were compared by group using the t test for independence. Grade 0 CASI was significantly more frequent for the no-dressing group (M = 3.91, SD = 1.514) in comparison to the dressing group (M = .83, SD = .937), t (16) = -5.78, p = .00. Grade 1 CASI was not significantly different between the no-dressing group (M = 2.09, SD = 1.514) and the dressing group (M = 2.08, SD = 1.929), t (21) = -.011, p = .992. Grade 2 CASI was significantly less frequent for the no-dressing group (M = .00, SD = .000) in comparison to the dressing group (M = 2.25, SD = 1.485), t (11) = 5.25, p = .00. Grade 3 CASI was not significantly different
between the no-dressing group (M = .00, SD = .000) and the dressing group (M = .58, SD = .996), *t*(11) = 2.03, *p* = .07. There were no grade 4 CASI episodes in either of the groups.

**Table 4.8 Frequencies of CASI grades for all observations for both groups combined**

<table>
<thead>
<tr>
<th>CASI Grade</th>
<th>Observations = 135</th>
<th>% Total CASI Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0 (No CASI)</td>
<td>53</td>
<td>39%</td>
</tr>
<tr>
<td>Grade 1</td>
<td>48</td>
<td>36%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>27</td>
<td>20%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>7</td>
<td>5%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Three scheduled CASI assessments were missed due to error (not included in total “n”)*

**Table 4.9 Frequencies of CASI grades for all observations by study group**

<table>
<thead>
<tr>
<th>CASI Grade</th>
<th>Dressing Group</th>
<th>No-Dressing Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observations = 69</td>
<td>% Total CASI Assessments</td>
</tr>
<tr>
<td>Grade 0 (No CASI)</td>
<td>10</td>
<td>15%</td>
</tr>
<tr>
<td>Grade 1</td>
<td>25</td>
<td>36%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>27</td>
<td>39%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>7</td>
<td>10%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Three scheduled CASI assessments were missed due to error (not included in total “n”)*

The groups were compared regarding presence of CASI of any grade at any assessment (Yes CASI) versus (No CASI). Two participants in the no-dressing group had no CASI at all assessments, whereas there were no participants in the dressing group that fell into this category. The result was not statistically significant, Fisher’s exact test, *p* = .217.

**4.9.3 CRBSI Incidence Density**

Due to the issue of missing DTP data, the BSI incidence density was calculated instead of the CRBSI incidence density, for both groups combined. The calculation of BSI incidence density was based on catheter days *during the study period* rather than from time of T-CVAD insertion. Although including all BSI events from time of T-CVAD insertion would have provided the most accurate picture of BSI incidence density, this approach would have entailed
extensive time-consuming chart review, which was outside the scope of this pilot study. The calculation of BSI incidence density did not include the data for the participant withdrawn prior to Week 1. The BSI incidence density for the study period was 1.01 per 1,000 catheter days.

4.9.4 Participant Preference Post Study (No-Dressing Group)

Participants in the no-dressing group were given the option to continue with no-dressing at the end of the study. Of the 11 participants who completed the study in the no-dressing group, 10 participants (91%) chose to continue with the no-dressing approach; one participant (9%) resumed the dressing approach.

4.10 Testing of Study Hypotheses

4.10.1 Primary Hypothesis (Difference in Mean CASI Episodes)

A two-way between-groups analysis of variance was conducted to test the hypothesis that mean CASI episodes would be greater for the dressing compared to the no-dressing group. Each finding of CASI (grade 1, 2, 3 and/or 4) was treated as one episode of CASI. The interaction between exposure to Busulfan pre HSCT (exposure or no exposure) and type of T-CVAD exit site care was also analyzed. As noted previously, participants were randomized prospectively into either a dressing or no-dressing group and stratified according to busulfan exposure.

Variance of the dependent variable (CASI) between groups was not statistically significant. The interaction between type of exit site care (dressing or no-dressing) and busulfan exposure (yes or no) was not statistically significant, $F(1, 19) = .86, p = .37$; however, there was a statistically significant main effect for type of T-CVAD exit site care (i.e. dressing or no-dressing), $F(1, 19) = .21.43, p = .00$. The effect size was medium, with partial eta squared = .53. As noted previously, the values for statistical significance and effect size are estimates only due to the small sample size.
4.10.2 Secondary Hypotheses

4.10.2.1 Relationship between Type of Exit Site Care and CASI ≥ Grade 2

A significant association between type of exit site care and CASI ≥ grade 2 was found, FET \((N = 23), p = .000\). The effect size was large with \(\phi = .917\). All participants in the dressing group had one or more episodes of CASI ≥ grade 2, whereas no participants in the no-dressing group had an episode of CASI ≥ grade 2.

4.10.2.2 Relationship between Type of Exit Site Care and CRBSI

It was planned a priori that DTP would be used to confirm CRBSI, as recommended by Safdar et al. (2005); however, this specification resulted in a situation where the endpoint of CRBSI could not be analyzed as defined because DTP data was incomplete for the one episode of BSI that occurred. As an alternative, the relationship between type of exit site care and BSI was tested. There was no significant association; the effect size was small, FET \((N = 23), p = 1.00, \phi = .204\).

4.10.2.3 Difference in CASI Episodes at Baseline Compared to End of Study

The McNemar’s test was used to test the hypothesis that there would be a greater proportion of CASI at the last study visit compared to baseline for the dressing group. No significant difference in number of CASI episodes was found between baseline and last study visit in the dressing group, McNemar’s exact test \((1, n = 12), p = 1.00\). The proportion of CASI episodes at baseline and end of study were also compared in the no-dressing group. A significantly smaller proportion of CASI episodes was found for the no-dressing group at end of study in comparison to baseline, McNemar’s exact test \((1, n = 11), p = .031\).
4.10.2.4 Post-Hoc Analyses of Clinical Variables Relevant to CASI and/or CRBSI

The following variables were identified in Chapter 2 as relevant factors that could possibly have a moderating effect on CASI and/or CRBSI in the allogeneic HSCT population: days of SCST; days of active skin GVHD; number of hospitalizations; mean ANC; days of follow-up, presence of fever (yes/no); presence of CVAD-related local infection (yes/no); relapse (yes/no); and death (yes/no). Post study homogeneity of variance between groups was tested to determine if these factors were balanced between the study groups. Continuous variables were evaluated using Levene’s test for equality of variances and the t test for equality of means. Homogeneity of variance was not statistically significant for any variable according to Levene’s test, except for number of hospitalizations, Levene’s test, $F = 4.419$, $p = .048$. There was one hospitalization in the dressing group and none in the no-dressing group. The mean values were not significantly different between groups for any of the variables according to the $t$ test for equality of means. The details of the $t$ test are provided in Table 4.10. Number of fever episodes, CVAD-related local infections, disease relapse, and death, were zero for both groups.

<table>
<thead>
<tr>
<th>Relevant Post Study Clinical Factors</th>
<th>Dressing N=12 (50%)</th>
<th>No-Dressing N=11 (50%)</th>
<th>$p$ value$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days skin GVHD, mean (SD)</td>
<td>3.33 (6.64)</td>
<td>4.0 (13.26)</td>
<td>.88</td>
</tr>
<tr>
<td>Days SCST, mean (SD)</td>
<td>15.08 (22.38)</td>
<td>17.45 (21.13)</td>
<td>.80</td>
</tr>
<tr>
<td>Hospitalizations, mean (SD)</td>
<td>.08 (.29)</td>
<td>.00 (.00)</td>
<td>.34</td>
</tr>
<tr>
<td>ANC, mean (SD)</td>
<td>3.38 (1.89)</td>
<td>3.66 (2.17)</td>
<td>.75</td>
</tr>
<tr>
<td>Days of follow-up, mean (SD)</td>
<td>44.00 (2.89)</td>
<td>41.82 (2.27)</td>
<td>.06</td>
</tr>
</tbody>
</table>

$^1$Equal variance not assumed.

4.11 Summary of Results

Although enrollment took longer to complete than originally projected, the accrual of 24 participants allowed for evaluation of all feasibility end points, including testing the study hypotheses. A wide range of feasibility elements was evaluated. The lower than expected
enrollment rate and longer than projected enrollment time proved to be the most logistically challenging aspects of the study. The Participant Feedback surveys provided an estimate of participant compliance with study procedures, ideas for improving study procedures, and insights into the experience of both using a dressing and having no-dressing. As hypothesized, the mean number of CASI episodes were found to be significantly greater for the dressing group in comparison to the no-dressing group and an association was found between type of exit site care and CASI > grade 2, with a large effect size for both of these findings. CASI episodes at the end of study compared to baseline were less for the no-dressing group, whereas no difference in episodes between baseline and end of study was found in the dressing group. The group difference in CRBSI events confirmed by DTP could not be tested as originally planned; however, the rate of BSI was found to be comparable. Notably, 91% of no-dressing participants chose to continue with no-dressing following their last study visit. In the next chapter the study results are discussed in relation to relevant evidence. Limitations and strengths of the study are described, and implications for nursing practice and future research are presented.
Chapter 5: Discussion

5.1 Introduction

The purpose of the pilot study was to evaluate the feasibility of conducting a prospective longitudinal RCT to compare dressing and no-dressing groups with respect to CASI episodes, CASI severity, and CRBSI rate in outpatient adult allogeneic HSCT recipients with embedded T-CVAD exit sites. To my knowledge, this pilot study is the first study to compare CASI between dressing and no-dressing groups of outpatient adult allogeneic HSCT recipients. The study provides evidence regarding the relationship between BSI and type of exit site care (dressing and no-dressing). In this chapter, the study results are discussed and compared to relevant published evidence. Limitations and strengths of the study are summarized, and implications for nursing and future research are described.

5.2 Discussion of Results

5.2.1 Enrollment

The low overall rate of enrollment in this pilot study (39%) represents a significant barrier to the completion of a large RCT comparing CASI and CRBSI for dressing and no-dressing groups in outpatient adult allogeneic HSCT recipients. The participation refusal rate in this pilot study of 58% is notably higher than the rate of 20% found by Shivnan et al. (1991) in their study comparing two different types of dressings in HSCT recipients; however, the Shivnan et al. study did not include a no-dressing group. This pilot study is the first to analyze enrollment rate, participation refusal rate, and time to complete enrollment in a prospective randomized study comparing dressing and no-dressing groups.
The eligibility criteria were assessed post-hoc to determine if some criteria were unnecessarily restrictive. Given the majority of criteria were designed to maximize participant safety it is not recommended that criteria requiring absence of fever and/or IV antibiotic use in the 7 days prior to enrollment be omitted in future RCTs of outpatient allogeneic HSCT recipients. Similarly, criteria requiring minimum T-CVAD duration of 40 days and embedding of the exit site were not found to be unduly restrictive, and are important to retain for safety reasons. Lack of access to professional medical translators was not a significant recruitment barrier in this pilot study; however, in a large-scale RCT it would be important to ensure the budget accommodated access to professional medical translators.

The reasons for refusing consent offered by prospective participants provided insight into the high refusal rate. The qualitative data highlight the anxiety faced by patients and their caregivers regarding the difficult and unpredictable recovery period post-transplant. The caution shown by prospective participants in this trial would likely be similar in a larger-scale RCT comparing dressing and no-dressing groups. The low enrollment rate highlights the importance of ensuring every potentially eligible individual receives an invitation to participate; however, the most effective strategy available to ensure completion of a large-scale RCT in a reasonable time period is likely a multi-site design. This strategy has been used successfully in other studies involving allogeneic HSCT recipients (Couban et al., 2016; Walker et al., 2016).

5.2.2 CASI Data Quality

The rate of missing CASI data overall was extremely low. This encouraging finding supports the ease of using the CASI Assessment Form and the Modified ECOG Skin Toxicity Scale in a busy clinical setting. The low missing data rate also demonstrates the importance of having multiple trained assessors. Although missing CASI data were not a logistical barrier, the
rate of discordant CASI grades (22%) is a concern. The discordant results during tandem assessment may have been due to gaps in assessor knowledge regarding the correct use of the Modified ECOG Skin Toxicity Scale or may represent limitations of the scale. Given the rate of discordant tandem results, the Modified ECOG Skin Toxicity Scale should undergo further testing prior to use in future research studies. The next step would be to evaluate the IRR of different assessor training protocols. If sub-optimal IRR is found with different training strategies tested, then the Modified ECOG Skin Toxicity Scale would need to undergo further revision and validation. Other important issues that need further evaluation are the optimal CBA boundary (i.e. 5 cm versus 7 cm diameter), and timing of assessment after dressing removal and antiseptic application (i.e. 15 minutes, 30 minutes, or other). Clinical experience suggests the CBA size should include skin impacted by additional adhesive applied when covering the dressing for showering, which extends the CBA to approximately 7 cm, and that the waiting time between removal of dressing and CASI assessment should reflect the time between the removal of the dressing and application of the new dressing that is followed in standard clinical practice, which is typically between 3 and 15 minutes. Using a 30-minute waiting time in research studies may lead to findings that are not transferable to clinical practice.

5.2.3 Data Quality in General

Feasibility thresholds were met regarding the data error rate and the overall missing data rate. The overall rate of missing clinical data was extremely low (<1%). There were feasibility issues identified with some specific data items, with the most significant concern related to missing DTP information for the one episode of BSI that occurred. Date of T-CVAD insertion was also problematic. Gaps were also identified with respect to dressing regimen data; however, overall the data items included in the pilot study proved to be relatively easy to access, and the
information collected was suitable for the descriptive analyses and testing the primary hypotheses, and two of three secondary hypotheses as planned. The low rate of missing data is an encouraging finding with respect to the feasibility of completing a high-quality large-scale RCT. The rate of missing data was higher for survey data than for clinical data. Survey data were missing due to non-completion of entire surveys rather missing data in surveys that were completed. In all cases of survey non-completion, the surveys were due on days I was not able to be at the clinic. This situation highlights the importance of having a study coordinator or assistant available to physically meet with participants when surveys are required. It would be necessary to include sufficient funding in study budgets to cover this cost. I found participants provided more information regarding the open-ended survey questions when I read the questions to them and recorded their answers verbatim; however, the drawback to this approach is that the participant may answer questions differently in the presence of a study team member.

5.2.4 Participant Withdrawal

The lower than expected withdrawal rate is an encouraging finding regarding the feasibility of a large-scale RCT comparing dressing to no-dressing groups in adult outpatient allogeneic HSCT recipients. Withdrawal rates were not reported in other prospective studies comparing dressing to no-dressing (Olson et al, 1995; Olson et al., 2004; Petrosino, et al., 1988).

5.2.5 Participant-Dependent Compliance

The Participant Feedback Surveys provided valuable insight into the reliability of patient-dependent procedures in this pilot study. The self-reported degree of compliance was higher for the no-dressing group based on mean scores of the Likert-type items and the qualitative feedback. The main element least adhered to in the dressing group was the use of the CeraVe™ cleanser. It may be that participants in the dressing group did not fully understand why they
were being asked to use CeraVe™ cleanser instead of their usual soap. The findings suggest that in a future RCT participants in the dressing group should use their usual soap to clean around the dressing for the following two reasons: (1) in standard practice, patients use the soap of their choice when cleaning the skin around their exit site dressing; and (2) asking the dressing participants to use CeraVe™ cleanser on the skin around their dressing appears to have unnecessarily complicated the showering procedure in that group. Participants in both groups commented they did not like using the CeraVe™ cleanser for reasons discussed previously. The findings from this pilot study suggest it would be beneficial to identify an alternative to CeraVe™ that is well-tolerated prior to the start of a new study to maximize consistency and compliance. Ongoing educational sessions with participants regarding study procedures would also be beneficial in a large-scale RCT to increase compliance. For participants who are not fluent in English, a professional medical translator should be present during educational sessions, a recommendation that has implications for budgeting with respect to future studies. Based on feedback from the participants, some of the no-dressing procedures should be modified. For example, the line drying procedure for no-dressing post showering could be simplified by using one sterile gauze pad instead of three.

5.2.6 Feedback from Participants Regarding Study Experience

There were several positive comments from the no-dressing participants about the absence of pruritus and/or rash around the exit site and the increased ease of showering. The high number of participants who expressed a preference for no-dressing at the end of the study supports the other study findings about potential benefits of no-dressing with respect to CASI. The qualitative data from this pilot study concurs with favorable remarks made by patients regarding no-dressing reported by Lawrence et al. (2014). In the Lawrence et al. report, no-
dressing was described as “less cumbersome”, and “a lot cleaner than the dirty bandage hanging there.” The finding that no-dressing is seen as beneficial by some patients supports designing a prospective fully-powered RCT to compare CASI between dressing and no-dressing groups.

5.2.7 Baseline Characteristics

Testing of baseline characteristics demonstrated there were no significant differences between the dressing and no-dressing groups, which demonstrated that the stratified block randomization approach was successful in balancing the two groups for important factors that may have had an influence on the dependent variables in the study. Using sealedenvelope.com (Sealed Envelope Ltd, 2017) to generate the randomization lists was straightforward, and there were no problems encountered in preparing and/or using actual sealed envelopes to assign participants to groups; however, in a large-scale potentially multi-centre study, a centralized automatic randomization system would be necessary to manage increased numbers of participants at different sites.

5.2.8 Descriptive Frequency Analyses

5.2.8.1 Dressing Regimen Characteristics

In this pilot study the TSM dressing with a border was used more frequently than the borderless type of TSM dressing, with a frequency of use of 81% and 19% respectively. This pattern of dressing use is consistent with the findings of an international survey of CVAD exit site dressing practice in 34 countries that was conducted by Broadhurst, Moureau, and Ullman (2016). These researchers also found greater frequency of use of the TSM dressing with a border (63.6%) and lower frequency of use of the borderless TSM dressing (30.7%). While the pattern of frequency of use between these two dressing types was consistent between the pilot study and the international survey, the TSM dressing with a border was used even more frequently in the
pilot study compared to the frequency of use reported by the Broadhurst, Moureau, and Ullman (2016) survey respondents (i.e. 81% versus 63.6%). The reason for this variation is unclear, but could be due to differences in institutional guidelines, availability and/or cost of dressing types, and nurse and/or patient preference.

5.2.8.2 CASI Details

The frequencies of CASI overall and by grade found in this pilot are similar to findings in other studies that included allogeneic HSCT recipients. The overall frequency of CASI in this pilot study was 61%, similar to the frequencies of 68% and 60% reported respectively by Shivnan et al. (1991) and Silveira et al. (2010) in their studies that included allogeneic HSCT recipients. Grade 1 CASI was found to be the most common type of CASI (36%) in this pilot study which is consistent with findings from studies conducted by Benhamou et al. (2002) and Rasero et al. (2000). The concurrence of findings regarding overall CASI frequency in this pilot study with findings in other studies supports viewing CASI as a substantial clinical problem in adult allogeneic HSCT recipients.

5.2.8.3 CRBSI Incidence Density

As discussed previously, it was not possible to report on CRBSI incidence density as originally planned. The BSI incidence density of 1.01 per 1,000 catheter days found in this pilot study was lower than the incidence density for CRBSI reported by Dix et al. (2012) and Keeler et al. (2015). This may be due in part due to differences in how CRBSI incidence density was defined and calculated in those studies, differences in central line care practice, and/or differences in study populations. The relatively low BSI frequency is not surprising in view of Howell et al.’s (1995) finding that neutropenia is a key independent variable influencing infection in long-term CVADs, and is consistent with the Olson et al. (1995) study where the
The majority of sepsis events occurred in neutropenic participants. The lack of neutropenic individuals in this pilot study may have played a role regarding the relatively lower rate of BSI but comparable evidence in the literature is lacking.

Increased understanding of the role of neutrophil status with respect to CRBSI for dressing and no-dressing in adult outpatient allogeneic HSCT recipients would be useful. In a large-scale RCT, a sub-group analysis could be planned a priori to learn more about the role of neutrophil status in CRBSI incidence density for a dressing group in comparison to a no-dressing group; however, very few allogeneic SCT recipients receiving follow-up care in the outpatient setting are neutropenic. In this pilot study, no individuals were excluded or withdrawn from the study due to neutropenia, highlighting the low degree of neutropenia in the outpatient allogeneic HSCT population. The nature of recruitment in this pilot study suggests that a very large number of participants would be needed to have sufficient power to test the difference in CRBSI incidence density for neutropenic and non-neutropenic outpatient allogeneic HSCT recipients in a comparison of dressing and no-dressing. Lack of reliable evidence regarding incidence density for CRBSI and risk factors for CRBSI in the outpatient allogeneic HSCT population represents a major gap in the literature.

5.2.8.4 Participant Preference (No-Dressing Group)

As noted in Chapter 4, 91% of participants in the no-dressing group chose to continue with no-dressing after finishing the study. This is a noteworthy result, despite the small sample size. Although the study refusal rate was high (58%), in part due to concerns about the no-dressing intervention, the experience of participants assigned to the no-dressing group appears to have been very positive based on preference to continue with this approach.
5.2.9 Testing of Study Hypotheses

Testing of the hypotheses confirmed that it was possible to collect the data required for analyses related to CASI. The difficulty in obtaining DTP information was a valuable feasibility finding for future study planning. Testing of the hypotheses confirmed the data base functioned well. In addition, useful information was generated regarding variability relevant for future study design.

5.2.9.1 Primary Hypothesis (Difference in CASI Episodes between Groups)

A $p$ value = .00 was calculated with respect to the difference in mean CASI episodes between dressing and no-dressing using two-way ANOVA. Although the $p$ value obtained is an estimate, this finding suggests that using no-dressing may be associated with fewer CASI episodes than using dressings. Unlike the Benhamou et al. (2002) study, busulfan was not shown to be a significant moderating factor with respect to CASI. It is important to recall the Benhamou et al. (2002) study included pediatric participants, while this pilot study was conducted with adults. The difference in study sample may explain the lack of interaction; however, the sample size of this pilot study is also too small to make conclusions about this issue. The lower number of CASI episodes found with no-dressing in this pilot study is consistent with studies that found less frequent CASI events with longer dressing change intervals (Benhamou, et. al., 2002). The finding of a medium effect size (partial eta squared = .53) between dressing approach and CASI episodes is not surprising given other evidence that dressings, dressing regimens and cleaning solutions play a major role in skin irritation and damage (Dykes, et al., 2001; Maki, Alvarado, & Ringer, 1991; Visscher et al., 2009; Waring et al., 2009); however, as confidence intervals were not calculated, the reliability of the effect size finding in this trial should be interpreted with caution.
5.2.9.2  Secondary Hypotheses

5.2.9.2.1  Difference in Episodes of CASI ≥ Grade 2 between Groups

The finding of a statistically significant association between type of exit site care and CASI ≥ grade 2 is important because CASI grade 2 or greater represents more serious and/or bothersome manifestations of CASI such as generalized pruritus, skin tears, and/or ulceration (Rasero et al., 2000). The large effect size found (ϕi = .917) provides some evidence supporting the relationship between type of exit site care (dressing or no-dressing) and CASI. Unfortunately, a comparison of these findings with existing literature is not possible due to the paucity of evidence in this area. Another noteworthy aspect of this analysis was the finding that no episodes of CASI ≥ grade 2 occurred in the no-dressing group.

5.2.9.2.2  Difference in Episodes of CRBSI between Groups

As described previously, BSI was compared between groups, instead of DTP-confirmed CRBSI. The analysis of this secondary end point demonstrated the logistical challenges of including DTP-confirmed CRBSI as a study end point. The lack of a significant relationship found between BSI and type of exit site care is consistent with other studies that have compared CRBSI and/or BSI between dressing and no-dressing groups (Keeler et al., 2015; Olson et al., 1995; Olson et al., 2004). In total, these results add weight to the argument that type of exit site care is not the primary factor in CRBSI. While this result is an important addition to the literature regarding the safety of no-dressing with respect to CRBSI, there are significant

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8The Olson, Gaudet, and Rennie (1995) publication was not located during the initial literature search, but was identified when the literature was consulted again following the study analysis. In the Olson, Gaudet, and Rennie (1995) study, 24 participants were randomized, and were stratified by gender and HSCT status (yes/no). In the dressing group, four of 11 participants developed sepsis compared to 13 in the no-dressing group, with the majority of sepsis cases occurring in neutropenic patients.
limitations with the pilot study, as well as the other studies cited. A large prospective RCT comparing CRBSI incidence density between dressing and no-dressing groups would provide important evidence.

5.2.9.2.3 CASI Episodes at Baseline in Comparison to End of Study

Using McNemar’s test to compare the proportion of patients with CASI at baseline to the end of study within groups, the proportion of patients with CASI at baseline and study completion was not significantly different in the dressing group. This intriguing finding contradicts some studies that found skin impairment increased with cumulative exposure to dressing adhesives and/or antiseptics (Shivnan et al., 1991; Silveira et al., 2010; Tokumura et al., 2005; Waring et al., 2011). In contrast, the proportion of patients with CASI was significantly different between baseline and study completion in the no-dressing group; this group had more episodes of CASI at baseline than at study completion. No comparable analyses have been published in the literature. This exploratory finding adds strength to the view that no-dressing is a promising strategy to reduce CASI and supports the argument that further research regarding no-dressing and CASI is necessary.

5.2.9.3 Post-Hoc Analyses of Clinical Variables

Post-hoc analysis for homogeneity of variance between study groups was conducted regarding variables that were identified a priori as potentially influencing CASI. The fact that homogeneity of variance was demonstrated between dressing and no-dressing with respect to days of skin GVHD, days of SCST, ANC, episodes of hospitalization, and days of study follow-up supports the validity of the findings in this pilot study regarding the hypotheses tested. These potentially moderating variables remain of interest and should be tested in future large sample
studies that compare CASI between dressing and no-dressing groups in the adult outpatient allogeneic HSCT population.

5.3 Safety

As discussed previously, the rate of BSI incidence density of 1.01 per 1,000 catheter days was lower in this pilot study in comparison to the CRBSI incidence density reported by Dix et al. (2012) and Keeler et al. (2015). The lower rate may be due to the absence of neutropenic participants; however, there is no evidence in the literature regarding differences in CRBSI or BSI rates between non-neutropenic and neutropenic allogenic HSCT recipients in the outpatient setting. One participant in the study experienced accidental egression of their T-CVAD. This participant was in the no-dressing group. With respect to accidental T-CVAD egression, there is a lack of published evidence regarding the incidence of this event. The frequency of accidental T-CVAD egression has not been reported in prospective studies comparing dressing and no-dressing groups (Olson et al., 1995; Olson et al., 2004; Petrosino et al., 1988).

5.4 Limitations

As with all pilot studies, the precision and validity of the statistical results generated were limited by the small sample size. The analytical plan for testing of the hypotheses did not include the calculation of interval estimates regarding effect sizes, which limits their usefulness for calculating power and sample size in a future large-scale RCT. Another limitation was the use of a CASI measurement tool that has not been tested for construct validity or IRR. While there was a high degree of consistency in terms of identifying CASI or no CASI, there was less reliability in the ability of the scale to distinguish between levels of severity (i.e. grades), as the majority of discordant results were due to different CASI grades being chosen by assessors. Although the nurse assessors were familiar with evaluating exit site skin condition as part of
their clinical practice, a formal grading tool had not been used before in the study setting. The findings suggest that the assessors needed more comprehensive training or that the scale needs further revision. Another limitation of this pilot study is that the actual number of participants who consented was considerably less than expected; therefore, the study sample may not accurately represent the true diversity of outpatient adult allogeneic HSCT recipients. It is possible individuals who declined to participate may have been more or less likely to develop CASI and/or CRBSI. The Participant Feedback Survey results indicated that participants did not always strictly follow the Participant Instructions regarding the care of their T-CVAD exit site during showering. The surveys were not validated prior to use in the study and can only be used as an estimate of compliance. The results suggest compliance was higher in the no-dressing group. The fact that there was some variation in compliance between the groups is a limitation regarding the validity of the study results.

5.5 Strengths

The pilot study has a number of strengths. The prospective RCT design of the study is a major strength. The analysis of variance between groups regarding key clinical factors at baseline and post-study suggests that the randomization process worked well to balance factors that might affect CASI and/or CRBSI. The low missing data rate (<1%) supports the validity of the results and the feasibility of conducting a large-scale RCT. The use of formal training sessions for the CASI assessors increased the robustness of the study. The scale diagram in the CASI Assessment Form was easy to use and contributed to the completeness and accuracy of data captured. The Modified ECOG Skin Toxicity Scale appears to have performed relatively well in a busy clinical environment, as shown by concordance of results for the majority of tandem assessments and a low rate of missing CASI data.
5.6 Implications for Clinical Practice

The findings of this pilot study cannot be used as a basis for change to standard clinical practice. In situations where CASI has been shown to be refractory to established dressing and/or antiseptic options available, the findings from this pilot study suggest that the use of no-dressing could be a viable option. Nonetheless, given its experimental status, no-dressing should be used with caution even in cases of refractory CASI.

5.7 Recommendations for Future Research

CASI is not a well-studied clinical phenomenon in allogeneic HSCT recipients, despite clinical evidence that it is a common problem. Given the findings of this pilot study, further research comparing dressing to no-dressing groups for effects on CASI requires development. A CASI-specific validated measurement tool is needed. The Modified ECOG Skin Toxicity Scale is the first tool that accounts for all the manifestations of CASI as defined by Broadhurst and Tardiff (2016). There are no other well-established validated tools for diagnosing and/or grading CASI available in the literature that can be compared to the Modified ECOG Skin Toxicity Scale to evaluate concurrent validity. Further evaluation of the Modified ECOG Skin Toxicity Scale as discussed in detail in Section 5.2.2 is necessary prior to its use in future studies of CASI.

Studies collecting empirical evidence regarding the incidence and prevalence of CASI in general and by levels of severity are necessary in the adult allogeneic HSCT population, both for inpatients and outpatients. Another important facet of CASI that requires further study is the relative role that dressings, cleaning solutions, and drying time play in the development of CASI. In order to study the relative impact of these variables one approach would be to use skin sites adjacent to the CBA rather than the CBA itself. By using multiple skin sites adjacent to the CBA concurrently, it would be possible to generate data for several different combinations of dressing
regimen conditions, including a control site, without increasing the risk of CASI and/or CRBSI. This is similar to the approach used by Visscher et al. (2009) in their study of the relative difference between dressing and antiseptic solutions in neonates with PICCs. In addition to these gaps in the scientific literature, it has been 5 years since Keeler’s (2014) survey of Canadian HSCT sites regarding T-CVAD exit site care. It would be beneficial to repeat this survey and extend the scope of the study to international HSCT centres.

CRBSI remains an important issue in studies that compare CASI between dressing and no-dressing groups. Comparing equivalence in a fully powered prospective trial has not been undertaken to date. Such a trial would require a very large number of participants due to the anticipated low rate of CRBSI; however, despite this challenge studies should be undertaken that examine CRBSI in outpatient allogeneic HSCT recipients. Another issue that needs to be addressed is whether to use CRBSI as the endpoint, or a less stringently defined endpoint such as central line-associated BSI (CLABSI) (O’Grady et al., 2011) or BSI. The likelihood of missing DTP data occurring in a large-scale RCT is high due to the unpredictable clinical course of allogeneic HSCT recipients. The wide variety of CRBSI criteria found in the literature reflects the ongoing dilemma that researchers face in defining and evaluating CRBSI (Safdar, et al., 2005; Maki, Kluger, & Crnich, 2006; O’Grady et al., 2011).

In terms of recommendations regarding statistical analysis, the use of two-way ANOVA proved to be effective in testing the primary research question posed in this pilot study; however, a multi-variate analysis would be necessary in a large-scale trial given the larger data set and many potentially moderating factors of relevance in the adult outpatient HSCT population. While testing with the McNemar’s exact test provided some preliminary evidence regarding the cumulative effect of dressing and no-dressing, there are statistical tests that could be employed to
more effectively evaluate this aspect of CASI such as repeated measure ANOVA. The analysis plan for testing of hypotheses should include the calculation of interval estimates regarding effect sizes in order to provide greater information regarding the precision of findings. It would be beneficial in a large-scale RCT to define and analyze parameters of clinical significance.

5.8 Conclusion

The feasibility analyses conducted demonstrated that several elements of the study functioned well, such as the randomization process, screening assessments, CASI Assessment Form, data collection, and the no-dressing procedure for line care; however, the significantly lower than expected rate of enrollment is a major potential barrier with respect to a large-scale RCT. Testing of the hypotheses provided important feasibility-related information with respect to variance and outcome measures. This pilot study is the first study to compare CASI between dressing and no-dressing groups in adult outpatient allogeneic HSCT recipients. In this pilot study, the no-dressing group demonstrated significantly fewer episodes of CASI, and a significant relationship was found between type of exit site care and moderate to severe CASI, with a greater proportion of moderate and severe CASI found in the dressing group. No relationship was found between exit site care type and BSI. As with all pilot studies, the findings were limited by a small sample size; however, the results provide support for developing a full-scale longitudinal RCT comparing CASI and CRBSI in outpatient adult allogeneic HSCT recipients. In order to complete such a trial, a multi-site approach could provide a solution to the low enrollment rate encountered in this pilot study.
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Appendices
Appendix A: Participant Information and Consent Form

CENTRAL VENOUS ACCESS DEVICE-ASSOCIATED SKIN IMPAIRMENT:
A PILOT STUDY COMPARING DRESSING TO NO-DRESSING IN ADULT ALLOGENEIC
STEM CELL TRANSPLANT RECIPIENTS

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For emergencies only: During regular clinic hours (i.e. 0700 to 1900 on weekdays and 0800 to 1600 on weekend and statutory holidays) call 604-875-4111, ext. 54073. Outside of regular clinic hours call 604-875-4111, extension 54343, and ask for the physician on call.

For non-emergency questions or concerns: Contact Holly Kerr at 604-875-4111, ext. 54073.
You are being invited to take part in this research study because you have had an allogeneic hematopoietic stem cell transplant (HSCT), you have a tunneled central venous access device (CVAD), and you are receiving care at the Leukemia/BMT Program of British Columbia Outpatient Daycare Unit (Krall Centre, Leon Judah Blackmore Pavilion, 6th Floor, A Side (LJBP6A), Vancouver General Hospital). The purpose of this research study is to evaluate the feasibility of conducting a larger study focused on the prevention of CVAD-associated skin impairment (CASI).

1. Terms you need to understand before reading this consent form

**Allogeneic hematopoietic stem cell transplantation:** A biological therapy in which an individual’s blood and immune cells are destroyed by total body irradiation and/or chemotherapy, followed by the infusion of healthy compatible immune and blood producing cells (i.e. hematopoietic cells) from another person.

**Central Venous Access Device (CVAD):** A plastic tube (i.e. catheter), used to deliver medications and blood products, inserted through the skin into a large peripheral vein and then moved along until the end of the tube is positioned at the entrance to the right atrium of the heart.

**Tunneled CVAD:** A plastic tube (i.e. catheter) inserted into the body through the skin, usually in the upper right chest area, and then tunneled under the skin through the fatty tissue for approximately 5 to 10 centimeters before it is inserted into a large peripheral vein in the neck area. Once the catheter is inserted into the large vein in the neck area it is moved along until the end of the tube is positioned at the entrance to the right atrium of the heart. A Hickman Line is an example of a tunneled CVAD.

**CVAD-associated skin impairment (CASI):** Skin damage within a 7 centimetre radius of a CVAD exit site that is due to mechanical, chemical, or microbiological injury.

**CVAD-related bloodstream infection:** A bloodstream infection linked to a CVAD rather than another source, such as the gut, oral mucosa or internal abscess.

**Pilot study:** A small study that is conducted in preparation for a large-scale study.

If you have any questions about these terms and/or the definitions provided, please ask the graduate student researcher for clarification.

2. Your participation is voluntary

Your participation is voluntary. You have the right to refuse to participate in this study. If you decide to participate, you can withdraw from the study at any time without negative consequences to your medical care, or other services.

You should be aware that there is a difference between being a patient and being a research participant. As a patient, all medical procedures, treatments, and nursing care are carried out for
your benefit only according to standard practice. As a research participant you are being asked to participate in a new approach to the care of your tunneled CVAD (i.e. Hickman Line) that is not part of standard practice at this unit. The study also involves some other procedures that are not standard practice. This consent form describes the procedures that are being carried out for research purposes. Please review the consent document carefully when deciding whether or not you want to be part of the research, and sign this consent only if you are comfortable being a research participant. If you want to participate in this study, you will be asked to sign this form. Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

3. Who is conducting this study?

This study is being conducted by a graduate student with the UBC School of Nursing under the direction of Dr. Wendy Hall of the UBC School of Nursing. A grant from the UBC School of Nursing has been awarded to cover costs associated with conducting this study; however neither UBC nor the hospital employees involved with this study are receiving personal payment for conducting this study.

4. Background

Skin impairment around the exit site of central venous access devices (CVADs) is a common problem in allogeneic transplant recipients. This complication occurs in about 46% to 68% of allogeneic transplant recipients, with symptoms ranging from mild skin redness to skin sores. This complication is referred to as “CVAD-associated skin impairment (CASI)”. The researchers are interested in conducting studies that are focused on decreasing CASI because this complication can result in itching, discomfort, and in some cases, more severe skin damage. Skin damage can increase the risk of infection.

In Canada, approximately 60% of transplant centres keep a dressing on an embedded (healed) tunneled CVAD exit site, whereas 40% of centres leave the exit site open to the air (i.e. no-dressing). A tunneled CVAD is considered to be embedded (healed) once the internal cuff has attached to fatty tissue under the skin and the suture has been removed. The reason for dressing an exit site prior to embedding is to decrease the risk of CVAD-related bloodstream infection; however, there is a lack of information demonstrating that dressing an embedded (healed) tunneled CVAD exit site reduces this risk. Three studies found the same rates of CVAD-related bloodstream infection between dressing and no-dressing in patients with long-term (i.e. embedded) tunneled CVADs, suggesting the risk may be the same.

Even though CASI is a recognized clinical problem, there have only been two studies conducted with the aim of decreasing this problem. In both of these studies, changing the dressing less often was compared to changing the dressing more often. A decrease in CASI was found when the dressing was changed less often, but CASI was not prevented entirely.

Dressings and antiseptic solutions (i.e. liquids used to eliminate microorganisms) may cause CASI. It is possible no-dressing may be effective in preventing and/or reducing the severity of
CASI without increased CVAD-related bloodstream infection risk, but this idea has never been tested in a research study.

At this centre, standard practice is to keep a dressing on a tunneled CVAD exit site from the time of insertion until the CVAD is removed. This study involves randomization to either a standard dressing group or a no-dressing group. A total of 26 participants will be enrolled. The study is being conducted at this hospital only. Participation in this study will last up to six weeks, and will involve short assessments of the skin condition around your CVAD exit site every seven days. The study will not involve extra visits to the clinic, and should not increase the length of your visit. You will be asked to follow some instructions regarding showering and the care of your tunneled CVAD exit site. At the end of the study you will be asked some questions regarding your experience in the study.

Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

5. **What is the purpose of the study?**

The purpose of the proposed pilot study is to evaluate the practical aspects of comparing no-dressing and dressing of embedded (i.e. healed) tunneled CVAD exit sites with respect to CASI rates, CASI severity, and CVAD-related bloodstream infection rates in outpatient adult allogeneic HSCT recipients. For example, a new standardized measurement tool that has been developed to identify and grade CASI will be evaluated for accuracy and ease of use.

This study involves a small number of participants and so it is not expected to prove safety or effectiveness. The results are intended to be used as a guide for planning larger studies, although there is no guarantee that larger studies will be conducted. Participation in this study does not guarantee you will be able to participate in a future larger study; however, knowledge gained from this study may be used to develop future studies that may benefit others.

6. **Who can participate in this study?**

You may be able to participate in this study if you are 19 years of age or older, have had an allogeneic transplant within the past 35 to 60 days, and have an embedded (healed) tunneled CVAD.

7. **Who should not participate in this study?**

You should not participate in this study if you have a history of endocarditis or abdominal abscess. You cannot participate if you have a CVAD other than a tunneled CVAD (i.e. you must have a CVAD like a Hickman Line™ to participate).

If you have an infection requiring intravenous therapy within the previous seven days you cannot participate in the study at this time, but you may be able to participate later. If you currently have an exit site suture and/or it has been less than 35 days since your transplant, then you
cannot participate at this time, but may be able to participate later. If you have active bleeding or discharge from your tunneled CVAD exit site or active serious skin impairment around your tunneled CVAD exit site you cannot participate in the study at this time, but you may be able to participate later if these issues resolve.

8. **What does the study involve?**

The first step is to read all the information in this consent form and to ask the researcher all the questions you have. It will take about one to two hours to read this consent form. Once you have received this consent form you will have up to seven days to ask questions and make your decision regarding whether or not you want to participate. If you sign this consent form it means you understand what the study involves and you want to participate. If you decide to consent to this study, the researcher will begin the screening process as described below.

**Screening**
The screening process will begin after you sign this consent form. The researcher will meet with you during one of your clinic visits to complete an assessment of your tunneled CVAD exit site, and ask you some questions about your medical history. This process will take approximately 15-20 minutes. You will not need to have any additional blood tests or other procedures as part of the screening process; however, the researcher will review information in your medical chart to ensure you are eligible. If you meet all the eligibility criteria then you will be randomized to one of the study groups within a day or two. If you do not meet all the eligibility criteria, you will not be able to participate in the study; however, the information that was collected for screening will be used by the researchers so they can estimate how long it would take to enroll patients in a larger trial.

**Randomization**
The randomization process is done using a computer program. You will be assigned to either the dressing group or the no-dressing group. The group you are assigned to is determined by chance, similar to tossing a coin. The researcher has no control regarding the study group you are assigned to. You have an equal chance of being assigned to either group. Once you have been assigned to one of these groups you are intended to stay in the group for the duration of the study; however, you can withdraw from the study at any time, and the care of your tunneled CVAD exit site will go back to standard practice at this centre.

Once you have been randomized to a study group, you have been formally enrolled in the study. After enrollment the researcher and/or a nurse at the outpatient unit (LJBP6A) will examine the skin around your CVAD exit site on a weekly basis for six weeks. The study assessment will take five to 10 minutes; however, this assessment should not extend the length of your clinic visit.

**Care of the tunneled CVAD applicable to both study groups**
As a participant in this study you will be asked to follow some instructions in order to ensure consistency between the two study groups with respect to CVAD care. You will be provided with a mild cleanser to use during showering (or sponge bathing). The cleanser will be provided
to you free of charge. You will be asked to have a sponge bath or shower every one to three days, and to wear clean clothes on a daily basis. You will be asked to wash your hands for 30 seconds prior to touching your CVAD. You will be asked to secure your CVAD by applying 2.5 cm wide waterproof tape to each lumen to form a tab just below the hard plastic segment of the lumen end. The tabs will need to be attached to a fabric necklace around your neck using two bulldog clamps that will be provided to you. **The CVAD exit site and external lines should never be submerged in water** (i.e. baths, swimming pools and/or hot tubs).

The CVAD lumens should be flushed and have new caps every seven or eight days according to the Vancouver General Hospital policies. A nurse will flush the line and change the caps while you are on the study.

**Care of the tunneled CVAD for the dressing group**

If you are assigned to the **dressing group** the following instructions apply to you. The care of your tunneled CVAD exit site will follow standard practice at this centre. If you have a Mepore™ (gauze) dressing you should only take sponge baths. If you have a Tegaderm IV Advanced Securement™ dressing or Tegaderm Diamond Pattern Film™ dressing you may shower, but must adhere to the following procedures. Your dressing and external CVAD line must be covered with a waterproof material (i.e. a plastic bag) and then taped to your skin around the edges to prevent your dressing and line from getting wet. The waterproof tape and cover should be removed immediately after showering. Your dressing will need to be changed according to the standard time interval at this centre. For Mepore™ (gauze) dressings, that is every two days. For Tegaderm™ dressing that is every seven or eight days; however, if the dressing appears to have become damp or wet, it should be changed as soon as possible. While you are on the study, a nurse must perform all dressing changes. If you think you need to change the dressing prior to a scheduled clinic visit, then you will need to call the outpatient clinic (LJBP6A) to discuss with one of the clinic nurses.

**Pictorial summary of showering process for the dressing group**

- The CVAD is placed in a plastic bag
- A knot is tied and the bag is flipped up
- The bag is positioned over the dressing and is taped in place
Care of the tunneled CVAD for the no-dressing group

If you are assigned to the no-dressing group the following instructions apply to you. You will be asked to leave your CVAD exit site uncovered (i.e. without a dressing or waterproof cover) during showering (or sponge bathing). You will need to keep the exit site out of the direct path of the shower stream during showering, except when you are rinsing the skin around the exit site after you clean it. To clean the area around the exit site, you will need to clean your hands for 30 seconds and then apply a small amount of cleanser to your index finger and thumb. You will then need to clean around the skin at the catheter exit site with your thumb and index finger for 30 seconds in an area within a 7 cm radius of the exit site. The exit site is rinsed in the shower stream for 15 seconds. After your shower (or sponge bath) you will need to dry your hands, and then dry the exit site, external plastic tube (catheter), connection points, and hub ends with sterile gauze sponges. You should wear clean clothes after showering. Once the line is dry and secured, no other special care is required; however, as noted above, the line should not be touched unless your hands are clean.

Pictorial summary of showering process for the no-dressing group

Skin within a 7 cm radius of the exit site is cleaned with a mild cleanser

The area is cleaned for 30 seconds

The exit site is rinsed for 15 seconds
Why is it important to follow the study procedures?
It is important to follow the study procedures for safety reasons, and also because the results of the study may be inaccurate if participants do not follow the study procedures. If at any time you feel that you do not want to adhere to the study procedures, you can withdraw from the study.

What else does this study involve?
At your last study visit you will be asked to complete a survey with seven questions about your experience in the study.

Will I be paid to participate in this study?
You will not be paid to participate in this study; however, if you are enrolled in the study, you will be provided with a gift card of $25 as a gesture of appreciation for your participation.

What information will be collected about me?
The researcher(s) will collect information that can be used to compare CASI and CVAD-related bloodstream infection between the two study groups, and information that can be used to plan a larger study focused on CASI. At the start of the study information about your medical history and the preparative regimen you received will be collected. Your age at the time of randomization and your gender will also be collected. Your white blood count and the severity of CASI (if present) will be collected at each visit.

What is the total amount of time this study will take in addition to standard follow-up?
It is estimated that participating in this study will take six hours of your time. Most of this time commitment will occur when you are at the clinic for your usual clinic visits.

9. What are my responsibilities?
Your main responsibility if you participate in this study will be to follow the study procedures. If for some reason you are not able to comply with the study procedures it is helpful to let the researcher know. If at any time you no longer wish to participate in the study, then you can withdraw from the study. Please let the researcher know if you would like to withdraw from the study.
10. **What are the possible harms and discomforts?**

As noted previously, the standard practice of dressing a tunneled CVAD exit site is associated with a risk of CVAD-associated skin impairment (CASI). The exact risk remains unknown as few large studies have been conducted regarding CASI. The risk of CASI for no-dressing is not known, as no studies have been conducted yet to determine this. Given that the main reason for maintaining a dressing on a tunneled CVAD exit site is prevention of CVAD-related bloodstream infection, it is important to consider the risk of CVAD-related bloodstream infection for both study groups. Three studies found the same rates of CVAD-related bloodstream infection between dressing and no-dressing; however, further research is needed to confirm this finding. The rate of CVAD-related bloodstream infection in adult allogeneic transplant recipients in general is estimated to fall between 2.03 to 7.6 per 1,000 catheter days. It is not anticipated that the rate of CVAD-related bloodstream infection will exceed this range for the people who participate in this study, although that cannot be guaranteed. All episodes of CVAD-related bloodstream infection that occur will be reported to the Director of Infection Control for Vancouver Coastal Health.

11. **What are the potential benefits of participating?**

No one knows whether or not you will benefit from this study. There may or may not be direct benefits to you from taking part in this study.

We hope that the information learned from this study can be used in the future to benefit other allogeneic transplant recipients with tunneled CVADs.

12. **What are the alternatives to this study?**

You can decide not to participate in this study. In that case, the care of your tunneled CVAD exit site will follow standard practice at this site, which involves maintaining a dressing on the exit site until your CVAD is removed, and covering the dressing and line with a waterproof material during showering.

13. **What happens if I decide to withdraw my consent to participate?**

You can withdraw from this study at any time. You do not have to provide reasons for withdrawing unless you want to. If you enter the study and then decide to withdraw at a later time, you have the right to request the withdrawal of your information that was collected for the study. If you withdraw your participation before the study has finished, the researchers can remove your data from the study; however, once the results have been analyzed, it will not be
possible to remove your data from the database. You do not have to return the study gift card if you choose to withdraw from the study.

If you would like to request the withdrawal of your data, please let the researcher know. The researcher will explain whether or not it is possible to withdraw your data. If not, the reason will be provided.

14. Can I be asked to leave the study?

You will be withdrawn from the study if your neutrophil count falls below $0.5 \times 10^9$ for more than seven days in a row, or you develop a fever of $38^\circ C$ or greater for more than three days in a row, or you are hospitalized for more than 14 days, and/or your medical doctor decides it is best for you to withdraw from the study. If you are not able to follow the requirements of the study, the researcher may withdraw you from the study and your CVAD exit site will be cared for according to standard practice. If you are asked to leave the study, the reason(s) will be explained, and you will have the opportunity to ask questions about this decision. Information that has been collected about you for the study will be included in the study analysis unless you do not agree. See the previous section regarding withdrawal of your study data.

15. How will my taking part in this study be kept confidential?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or her designate by representatives of the University of British Columbia Research Ethics Board (CREB) or Vancouver Coastal Health for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study code as a participant in this study. This code will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.). Only this code will be used on research-related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected. You also have the legal right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor. Your data will not be transferred outside of Canada.
Should we notify your primary care physician about your participation in this study?

Your personal information or information that could identify you will not be revealed without your express consent unless required by law.

Please indicate, by checking the applicable box below, whether you want us to notify your primary care physician(s) of your participation in this study. This is not a consent to release medical information.

☐ Yes, I want the study investigator to advise my primary care physician(s) of my participation in this study. My primary care physician(s) is/are: ____________________________

The name of the medical clinic I attend is: ____________________________

Participant Initials: ________

☐ No, I do not want the study investigator to advise my primary care physician(s) of my participation in this study.

Participant Initials: ________

☐ I do not have a primary care physician or specialist.

Participant Initials: ________

You may wish to discuss the consequences of your decision with the study staff.

Disclosure of gender
The researcher would like to collect information regarding your gender as it is possible this characteristic may impact CASI.

16. What happens if something goes wrong?

By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan.

17. What will the study cost me?

It will not cost you any money to participate in this study. The supplies you need to participate in the study, such as the cleanser, plastic bags, waterproof tape and/or sterile gauze sponges will
be provided to you at no cost. You will not be required to make any extra visits to the clinic, so there will not be any additional expenses associated with this study such as parking.

18. Who do I contact if I have questions about the study during my participation?

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact Holly Kerr at 604-875-4073 or Dr. Wendy Hall at 604-822-7447.

19. Who do I contact if I have any questions or concerns about my rights as a participant?

If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics by e-mail at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free: 1-877-822-8598).

20. After the study is finished

After the study you should discuss the ongoing care of your CVAD exit site with one of the transplant doctors on the outpatient transplant Unit (LJB6A). If you were in the no-dressing group you can continue with this approach to exit site care if the transplant doctor agrees that is a suitable plan for you. If you were in the dressing group, you will need to continue with that approach as dressing is the standard care at this centre.
21. Informed Consent Signature Page

By signing this consent form below, you are agreeing to participate in the study:
*Central Venous Access Device-Associated Skin Impairment: A Pilot Study Comparing Dressing to No-Dressing in Adult Allogeneic Stem Cell Transplant Recipients*

**Participant Consent**

My signature on this consent form means:

- I have read and understood the information in this consent form.
- I have had enough time to think about the information provided.
- I have been able to ask for advice if needed.
- I have been able to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific purposes.
- I understand that my participation in this study is voluntary.
- I understand that I am completely free at any time to refuse to participate or to withdraw from this study at any time, and that this will not change the quality of care that I receive.
- I authorize access to my health records as described in this consent form.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits to me.
- I understand I will receive a signed copy of this consent form for my own records.

I consent to participate in this study:

<table>
<thead>
<tr>
<th>Participant’s Signature</th>
<th>Printed name</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Signature of Person Obtaining Consent</th>
<th>Printed name</th>
<th>Date</th>
</tr>
</thead>
</table>

Study Role: ______________________

Was the participant assisted during the consent process in one of ways listed below?

☐ Yes  ☐ No

If yes, please check the relevant box and complete the signature space below:
☐ The consent form was read to the participant, and the person signing below attests that the study was accurately explained to, and apparently understood by, the participant (please check if participant is unable to read).

☐ The person signing below acted as an interpreter/translator for the participant, during the consent process (please check if an interpreter/translator assisted during the consent process).

____________________  __________________  __________
Signature of Person Assisting with Consent   Printed name   Date

Study Role: __________________________
Appendix B: Letter of Invitation to Participate

Date:

Dear Patient,

Re: Research Study:  
Central Venous Access Device Associated Skin Impairment: A Pilot Study Comparing Dressing to No-Dressing in Adult Allogeneic Stem Cell Transplant Recipients

We are writing to inform you of a pilot study comparing no-dressing of tunneled CVAD exit sites to dressing of tunneled CVAD exit sites. No-Dressing means the CVAD exit site is left uncovered. This is the experimental part of the study. Dressing means the CVAD exit site is covered with a dressing at all times. Dressing is the usual practice at this centre. Sometimes skin damage can occur around the exit site when dressings are used. This is called CVAD-associated skin impairment (CASI).

The principal investigator of the research study, Dr. Wendy Hall, is a professor at the UBC School of Nursing.

By conducting this small pilot study, we hope to learn ways to improve the way we identify and measure CASI. The information gained from this study will be useful for planning larger studies that will be able to test if no-dressing is a better way to take care of CVAD exit sites.

For more information about the study or to arrange for your participation, contact Dr. Hall at 604-822-7447 or the graduate student researcher Holly Kerr R.N. at 604-875-4073.

Participation in the study is voluntary. If you choose not to participate, your care will not be affected in any way.

The graduate student researcher (Holly) will contact you regarding your interest in this study in the next two weeks. If you do not want any further contact regarding this study, please contact Holly at 604-875-4073 or Janice Ha at 604-875-4111 ext. 64192.

Sincerely,

Janice Ha, RN, BScN  
Patient Services Manager  
Leukemia/BMT Outpatient Clinics and Daycare, Hematology Apheresis Unit, and Thrombosis Clinic  
Vancouver General Hospital
## Appendix C: Screening Log

<table>
<thead>
<tr>
<th>Screening Code</th>
<th>Date Invited to Participate</th>
<th>Day Post CVAD Insertion</th>
<th>Date of Consent or N-A</th>
<th>Eligible Yes or N-A</th>
<th>Enrollment Date or N-A</th>
<th>Study Code or N-A</th>
<th>Reason for No Consent or N-A</th>
</tr>
</thead>
<tbody>
<tr>
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Page ____ of ____
Appendix D: Standard Practice Dressing Regimen Algorithm (Study Site)

T-CVAD insertion

- Mepore™ gauze dressing until bleeding and/or discharge resolve
- CHX-ETOH cleaning solution
- Skin preparation solution

Resolution of bleeding and/or discharge AND no evidence of skin irritation

- Tegaderm IV Advanced Securement Dressing™ small (TSM dressing)
- CHX 2% in ETOH 70% cleaning solution
- Skin preparation solution

No evidence of skin irritation

Skin irritation (as per RN judgement)

Resolution of bleeding and/or discharge WITH skin irritation (as per RN clinical judgement)

- Tegaderm IV Advanced Securement Dressing™ small (TSM dressing)
- CHX 2% cleaning solution (NO ETOH)
- Skin preparation solution

No evidence of skin irritation

Skin irritation (as per RN judgement)

- Tegaderm IV Advanced Securement Dressing™ small (TSM dressing)
- Povidone-iodine 10% cleaning solution
- Skin preparation solution

No evidence of skin irritation

Skin irritation (as per RN judgement)

- Tegaderm Diamond Film™ dressing
- Povidone-iodine 10% cleaning solution
- Skin preparation solution

No evidence of skin irritation

Skin irritation (as per RN judgement)

- Foam dressing (Allevyn or Mepilex)
- Povidone-iodine 10%
- Skin preparation solution

No evidence of skin irritation

If skin irritation continues, consult Infusion Team or Educator

*If at any time open areas occur, consult Infusion Team or Program Educator
Appendix E: Procedures for Dressing Application and Removal

The Mepore™ dressing was applied as follows: (1) the two sides of the liner were peeled back on both sides so that the adhesive surface of the middle third of the dressing is exposed; (2) the exposed adhesive surface was positioned so that it was centred over the exit site and then fingers were used on the non-adhesive surface of the dressing to firmly press the middle third of the dressing onto the skin; (3) the remaining liner was then peeled off; (4) the fingers were used to firmly press the remaining adhesive surface of the dressing onto the skin (Mölnlycke Health Care, 2017). The Tegaderm IV Advanced Securement™ dressing was applied as follows: (1) the inner portion of the liner was peeled off the dressing to expose the adhesive surface; (2) the transparent portion of the dressing was positioned so that it was centred over the exit site while holding the notched portion off the skin; (3) the two sides of the notched portion of the dressing were positioned so the sides fit snugly around the catheter; (4) the fingers were used to press the dressing firmly into place; (5) the remaining outer portion of the liner was then peeled off; (6) one of the sterile tapes provided with the dressing was placed under the catheter lumen in a horizontal position; (7) the second sterile tape provided was placed over the catheter lumen in a horizontal position (Healthcare 3M, 2010; VCHA, 2017). The Tegaderm Diamond Pattern Film™ dressing was applied as follows: (1) the central portion of the liner was removed to expose the adhesive; (2) the adhesive side of the dressing was positioned to face the skin with the exit site in the middle and the split in the external liner frame positioned over the catheter; (3) the dressing was pinched in place around the catheter at the split in the external liner; (4) the dressing was then pressed onto the skin, and the external liner frame peeled away (Healthcare 3M, 2011). As per manufacturers’ instructions, care was taken not to stretch the dressings as
they were applied to the skin (Healthcare 3M, 2010; Healthcare 3M, 2011; Mölnlycke Health Care, 2017).

Mepore™ dressings were removed by loosening one edge and slowly peeling the dressing from the skin in the direction of hair growth (Mölnlycke Health Care, 2017). The Tegaderm IV Advanced Securement™ dressing was removed as follows: (1) the tape strips on top of the dressing were removed; (2) the stabilization tabs were separated and the dressing was gently peeled back towards the exit site; (3) the dressing was slowly peeled back over itself while stabilizing catheter and supporting surrounding skin; (4) adhesive remover was used if necessary. (Anderson, 2010; Health Care 3M Canada, 2010; VCHA, 2017). The Tegaderm Diamond Pattern Film™ dressing was removed as follows: (1) the dressing was slowly peeled back over itself; (2) the dressing was not lifted upwards during peeling; (3) the catheter and surrounding skin were stabilized during the peeling process (Health Care 3M Canada, 2011).
Appendix F: Participant Instructions (Dressing Group)

Showering Instructions

SUPPLIES:
- Cavi™ wipes (1-2)
- Blue gloves (2)
- Plastic bag (1)
- Pink waterproof tape 3.5 cm wide (1 roll)
- CeraVe Hydrating Cleanser™ for normal to dry skin (1)
- Work surface (i.e. counter top or portable tray)
- Clean hand towel
- Clean clothes

*Cavi™ wipes, blue gloves, plastic bags, pink waterproof tape, and CeraVe Hydrating Cleanser™ for normal to dry skin will be provided at no charge. If you are running low of supplies, please ask one of the clinic nurses for more.*

IMPORTANT POINTS:
- CeraVe Hydrating Cleanser™ for normal to dry skin should be used for personal hygiene while on study
- The external portion of the CVAD should only be touched with clean hands, defined as hands that have been washed with soap and water for 30 seconds
- Shower every 1 to 3 days
- Limit showers to 25 minutes
- If you find your dressing has become moist or wet, phone the Leukemia/BMT Outpatient Unit and speak with a nurse for further instructions
- Do not submerge your exit site in water (i.e. in a bath tub or a swimming pool)
- Wear clean clothes each day, if possible

Steps for cleaning your exit site and external CVAD:

1. Put on blue gloves and clean work surface with a Cavi™ wipe
2. Remove gloves and wash hands for 30 seconds with CeraVe Hydrating Cleanser™
3. Place clean hand towel, baggy and waterproof tape on the clean work surface
4. Place external CVAD into plastic bag

5. Tie top of bag together using a knot that can be untied later

6. Flip bag up so it is folded in half

7. Position folded plastic bag over the exit site dressing

8. Tape the bag in place with the pink waterproof tape

9. Check for gaps in the tape seal – Fix as necessary
Appendix G: Participant Instructions (No-Dressing Group)

Cleaning Your Exit Site and External CVAD

SUPPLIES:
- Cavi™ wipes (1-2)
- Blue gloves (2)
- Clean hand towel (1)
- Clean bath towel (1)
- CeraVe Hydrating Cleanser™ for normal to dry skin (1)
- Individually wrapped 2 cm x 2 cm sterile gauze sponges (2)
- Individually wrapped 4 cm x 4 cm sterile gauze sponge (1)
- Work surface (i.e. countertop or portable tray)
- Clean clothes

*Cavi™ wipes, blue gloves, sterile gauze, and CeraVe Hydrating Cleanser™ for normal to dry skin will be provided at no charge. If you are running low of supplies, please ask one of the clinic nurses for more.*

IMPORTANT POINTS:
- CeraVe Hydrating Cleanser™ for normal to dry skin should be used for personal hygiene while on study
- The external portion of the CVAD should only be touched with clean hands, defined as hands that have been washed with soap and water for 30 seconds
- Shower every 1 to 3 days
- Limit showers to 25 minutes
- Do not submerge your exit site in water (i.e. in a bath tub or a swimming pool)
- Wear clean clothes each day, if possible

Steps for cleaning your exit site and external CVAD:
7. Apply one pump of CeraVe Hydrating Cleanser™ to index finger

8. Place index finger with cleanser at the exit site – Hold catheter away from body with other hand

9. Gently rub cleanser back and forth around the exit site within a 7 cm radius of the exit site as shown in the next panel

10. Clean the exit site area for 30 seconds

11. Rinse exit site in the shower for 15 seconds (until suds are gone)

12. Turn away from the shower stream so exit site and CVAD are not in the direct path water for remainder of shower

13. Step out of shower when done

14. Dry hands and upper body with the hand towel – Avoid touching exit site area – Dry rest of body with the bath towel

15. Use one 2 x 2 gauze to dry exit site

16. Use the 2nd 2 x 2 gauze to dry the catheter

17. Use the 4 x 4 gauze to dry connection points and hub ends

18. Secure tabs

Start at centre
Pat dry – outwards in a circular direction until 7 cm from centre
Appendix H: CASI Assessment Form

<table>
<thead>
<tr>
<th>Date: __________ __________ __________</th>
<th>Place addressograph here:</th>
</tr>
</thead>
</table>

**Screening only:**
- Tug Test (circle):
  - Movement
  - No Movement

- Time cleaning finished: __________ or N/A
- Time of Assessment: __________

- **Pruritus (circle):**
  - Yes
  - No

- **Discharge (circle):**
  - Yes
  - No

- **Screening only:**
  - Suture at ES (circle):
    - Yes
    - No

- Check all symptoms present 15 minutes after cleaning site (dressing) or at time of assessment (no-dressing).
- Mark area(s) of skin affected on CBA diagram (above) using abbreviations shown in brackets below

<table>
<thead>
<tr>
<th>Skin normal &amp; intact</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus (P)</td>
<td>Erythema (ER)</td>
</tr>
<tr>
<td>Edema (E)</td>
<td>Induration (IN)</td>
</tr>
<tr>
<td>Papular rash (PAP)</td>
<td>Tenderness/pain (PA)</td>
</tr>
<tr>
<td>Macular rash (MAC)</td>
<td>Discharge</td>
</tr>
<tr>
<td>Shiny skin (SS)</td>
<td>Maceration (skin appears grey, white and/or wrinkled) (M)</td>
</tr>
<tr>
<td>Vesicles (V)</td>
<td>Bullae (BU)</td>
</tr>
<tr>
<td>Skin tear(s) (ST)</td>
<td>Exfoliative dermatitis (ED)</td>
</tr>
<tr>
<td>Folliculitis (F)</td>
<td>Ulcerating dermatitis (UD)</td>
</tr>
</tbody>
</table>

- Within 2 cm ES
- Along tunnel track
**Dressing Change Information**

<table>
<thead>
<tr>
<th>REASON FOR CHANGE:</th>
<th>DRESSING REMOVED:</th>
<th>DRESSING APPLIED:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Routine</td>
<td>□ Tegaderm IV Adv Sec</td>
<td>□ Tegaderm IV Adv Sec</td>
</tr>
<tr>
<td>□ Dressing loose</td>
<td>□ Mepore</td>
<td>□ Mepore</td>
</tr>
<tr>
<td>□ Dressing missing</td>
<td>□ Gauze (4x4) &amp; paper tape</td>
<td>□ Gauze (4x4) &amp; paper tape</td>
</tr>
<tr>
<td>□ Dressing soiled</td>
<td>□ Allevyn</td>
<td>□ Allevyn</td>
</tr>
<tr>
<td>□ Blood</td>
<td>□ Tegaderm Diamond Film</td>
<td>□ Tegaderm Diamond Film</td>
</tr>
<tr>
<td>□ Drainage</td>
<td>□ Other:</td>
<td>□ Other:</td>
</tr>
<tr>
<td>□ Damp or Wet</td>
<td>□ No-Dressing</td>
<td>□ No-Dressing</td>
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<tr>
<td>□ CASI</td>
<td></td>
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<tr>
<td>□ Other reason:</td>
<td></td>
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<tr>
<td>□ Unknown</td>
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</tr>
</tbody>
</table>

**Modified ECOG Skin Toxicity Scale Rating**

Grade (circle one)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
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<tr>
<td>1</td>
<td>Scattered macular eruption, or scattered papular eruption, or asymptomatic erythema, or scattered pruritus</td>
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<tr>
<td>2</td>
<td>Scattered macular eruption <em>with pruritus</em>, or scattered papular eruption <em>with pruritus</em>, or erythema <em>with pruritus</em>, or scattered vesicular eruption, or scattered folliculitis, or scattered induration, or maceration, or generalized pruritus, or shiny skin</td>
</tr>
<tr>
<td>3</td>
<td>Generalized macular eruption, or generalized papular eruption, or generalized vesicular eruption, or generalized folliculitis, or generalized induration (including induration along the tunnel tract), or bulla(e), or skin tear(s) &lt; 10% CBA, or pain, or discharge, or <em>microbiologically documented CRLI</em></td>
</tr>
<tr>
<td>4</td>
<td>Exfoliative dermatitis or ulcerating dermatitis, or ruptured bulla(e), or skin tear(s) ≥ 10% CBA</td>
</tr>
</tbody>
</table>

**DEFINITIONS:**

- **Scattered:** < 25% CBA
- **Generalized:** ≥ 25% CBA
- **No CBA area specified:** If a sign or symptom is not described as “scattered”, or “generalized” or a specific CBA percentage, then it can be assumed that “any area” of the sign or symptom within the CBA is intended.
- **Microbiologically documented CRLI:** Localized infection occurring within 2 cm of a CVAD exit site and/or along the tunnel tract, characterized by tenderness, erythema, induration, and/or purulent discharge, with or without fever, and confirmed by microbiological testing (Mermel et al., 2009).

If form not completed at scheduled assessment time point, please indicate the reason:

- □ N/A
- □ Participant refused
- □ Participant in hospital
- □ Lack of participant time
- □ Lack of nurse time
- □ Other

Form completed by: ______________________________ Date: __________________

Page 2 of 2
Appendix I: Participant Feedback Survey (Dressing Group)

Date: |____|____|____|____|____|____|

Participant Code: |____|____|

Your answers will help the researchers improve the instructions for participants in future studies.

There is no right or wrong answer!

Your answers are voluntary. If you prefer not to answer a particular question, then please leave it blank.

Thanks for your time completing this survey!

(1) **Did you use CeraVe Hydrating Cleanser when showering?** (circle one)

   All the time
   Most of the time
   Sometimes
   Rarely
   Never

(2) **If you answered sometimes, rarely or never, please explain why you did not use this cleanser:**

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

(3) **During the study I showered:** (circle one):

   Daily
   Every 2\textsuperscript{nd} day
   Every 3 days
   Less often than every 3 days
   It varied a lot
(4) **How often were you able to follow the instructions regarding “keeping your dressing and central line dry during showering”?** (circle one)

All the time
Most of the time
Sometimes
Rarely
Never

(5) **How often do you think your dressing became damp or wet during showering?**

All the time
Most of the time
Sometimes
Rarely
Never

(6) **Were there any participant instructions that you felt were too restrictive?** Please provide more information below:

_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

(7) **Please provide any other feedback you would like to share with the researchers:**

_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________
Appendix J: Participant Feedback Survey (No-Dressing Group)

Date: [___-___-____]  [___-___-____]  [___-___-____]  [___-___-____]

Participant Code: [___-___-___-___]

Participant Feedback Survey (No-Dressing)

Your answers will help the researchers improve the instructions for participants in future studies.

There is no right or wrong answer!

Your answers are voluntary. If you prefer not to answer a particular question, then please leave it blank.

Thanks for your time completing this survey!

(1) Did you use CeraVe Hydrating Cleanser™ when showering? (circle one)

All the time

Most of the time

Sometimes

Rarely

Never

(2) If you answered sometimes, rarely or never, please explain why you did not use this cleanser:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

(3) During the study I showered: (circle one):

Daily

Every 2nd day

Every 3 days

Less often than every 3 days

It varied a lot
(4) **How often were you able to follow the 4 steps regarding how “to clean the area around the exit site” when in the shower** (i.e. wash hands for 30 seconds, etc)? (circle one)

- All the time
- Most of the time
- Sometimes
- Rarely
- Never

(5) **How often were you able to follow the 5 steps regarding what to do “once you finished your shower”** (i.e. dry your hands with a clean towel, open two sterile 2 x 2 gauze, etc) (circle one)

- All the time
- Most of the time
- Sometimes
- Rarely
- Never

(6) **Were there any participant instructions that you felt were too restrictive?** Please provide more information below:

_______________________________________________________________________

_______________________________________________________________________

_______________________________________________________________________

(7) **Please provide any other feedback you would like to share with the researchers:**

_______________________________________________________________________

_______________________________________________________________________

_______________________________________________________________________
### Appendix K: Summary of Study Procedures

<table>
<thead>
<tr>
<th>Study Procedures</th>
<th>Day 35-60 p</th>
<th>Day 0</th>
<th>Day 7 W 1</th>
<th>Day 14 W 2</th>
<th>Day 21 W 3</th>
<th>Day 28 W 4</th>
<th>Day 35 W 5</th>
<th>Day 42 W 6</th>
<th>End of Study^2</th>
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^1Participants permitted to miss up to two CASI assessments.

^2End of study visit is Day 42 for participants who complete the full six week follow-up or day of last CASI assessment completed in case of withdrawal prior to Week 6.
Appendix L: Data Collection Forms (DCFs)

RANDOMIZATION

1.1 PARTICIPANT SCREENING CODE: [___]

1.2 PARTICIPANT’S YEAR OF BIRTH: [___________]

1.3 Date of screening visit: [___-___-______]

1.4 ASSESSMENT OF ELIGIBILITY (tick all boxes that apply)

- Be 19 years of age or over
- Be the recipient of an allogeneic HSCT (sibling, haploidentical or unrelated donor) within the past 35-60 days (Day post HSCT: _____)
- Be receiving post-allogeneic HSCT follow-up care in the VGH outpatient HSCT clinic
- Have an indwelling tunneled CVAD with cuff (either Hickman™, Leonard™ or Broviac™)
- Have an embedded T-CVAD (as per glossary) inserted > 40 days previous to screening visit
- Have documented neutrophil engraftment as defined in the glossary
- Be free of temperature > 38° Celsius in the previous 7 days
- Have a Modified ECOG Skin Toxicity Scale grade of < 4 within 7 cm of the T-CVAD exit site
- Be able to provide informed consent

At the time of enrollment, the participant must not:

- Have an infection requiring systemic IV therapy within previous 7 days
- Have a history of abdominal abscess or endocarditis
- Have active discharge and/or bleeding from the T-CVAD exit site
- Have a Modified ECOG Skin Toxicity Scale grade > 3
- Have a non-tunneled CVAD

1.5 Does the participant fulfill all of the eligibility criteria?

[___] Yes: Complete Item 1.6 (RANDOMIZATION)

[___] No: DO NOT RANDOMIZE

1.5.1 PARTICIPANT ALPHANUMERIC CODE: [_______-______]

1.5.2 Date of randomization: [___-___-______]

1.5.3 Study group assignment (circle one): DRESSING NO-DRESSING

Signature of person completing the randomization: _________________________________
SECTION 1: SCREENING (BASELINE DATA – PART A)

1.1 Date of consent: [DD] [MMM] [YYYY]

1.2 Screening visit date: [DD] [MMM] [YYYY]

1.3 Age: [__ __]

1.4 Date of allogeneic HSCT: [DD] [MMM] [YYYY]

1.5 Donor type regarding most recent HSCT:
   - [ ] Sibling
   - [ ] Haploidentical
   - [ ] Volunteer unrelated donor

1.6 Preparative regimen:
   - [ ] Yes – Busulfan
   - [ ] No – Busulfan

1.7 Date of transition from inpatient HSCT unit to outpatient unit: [DD] [MMM] [YYYY]

1.8 Type of CVAD (only individuals with T-CVADs are eligible for the study):
   - [ ] Tunneled (Hickman™, Broviac™, Leonard™)
   - [ ] Other*: _______________________________

1.9 Date of T-CVAD insertion: [DD] [MMM] [YYYY]

1.10 Date of T-CVAD suture removal: [DD] [MMM] [YYYY] Or
   - [ ] Date unknown; NO suture at screening assessment
   - [ ] Suture present at screening visit

1.11 Status of T-CVAD exit site at screening visit:
   - [ ] Embedded (Tug test negative; no suture)
   - [ ] Not embedded
   - [ ] Extruded (cuff showing)

1.12 Presence of bleeding and/or drainage from T-CVAD exit site at screening visit:
   - [ ] Yes
   - [ ] No
SECTION 1: SCREENING (BASELINE DATA – PART A) (continued)

Most recent WBC results within the past 7 days of screening visit:

1.13 Total WBC: \( \_\_\_\_\_\_\_\times10^9/L \)

1.14 ANC: \( \_\_\_\_\_\_\_\times10^9/L \)

1.15 Date CBC specimen collected: \( \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \)

1.16 History of temperature \( \geq 38^\circ \) Celsius with the past 7 days:

☐ Yes
☐ No

1.17 Infection requiring systemic IV therapy within 7 days prior to screening visit:

☐ Yes
☐ No

1.18 History of abdominal abscess:

☐ Yes
☐ No

1.19 History of endocarditis:

☐ Yes
☐ No

1.20 CASI grade assessment #1:

☐ 0 None
☐ 1 Scattered macular eruption, or scattered papular eruption, or asymptomatic erythema, or scattered pruritus
☐ 2 Scattered macular eruption with pruritus, or scattered papular eruption with pruritus, or erythema with pruritus, or scattered vesicular eruption, or scattered folliculitis, or scattered induration, or maceration, or generalized pruritus, or shiny skin
☐ 3 Generalized macular eruption, generalized papular eruption, or generalized vesicular eruption, or generalized folliculitis, or generalized induration (including induration along the tunnel tract), or bulla(e), or skin tear(s) \( \leq 10\% \) CBA, or pain, or discharge, or \textit{microbiologically} documented CRL1
☐ 4 Exfoliative dermatitis, or ulcerating dermatitis, or ruptured bulla(e), or skin tear(s) \( > 10\% \) CBA
1.21 Was a tandem CASI assessment done?

☐ Yes
☐ No

1.22 CASI grade assessment #2 (i.e. tandem assessment):

☐ 0 None
☐ 1 Scattered macular eruption, or scattered papular eruption, or asymptomatic erythema, or scattered pruritus
☐ 2 Scattered macular eruption with pruritus, or scattered papular eruption with pruritus, or erythema with pruritus, or scattered vesicular eruption, or scattered folliculitis, or scattered induration, or maceration, or generalized pruritus, or shiny skin
☐ 3 Generalized macular eruption, generalized papular eruption, or generalized vesicular eruption, or generalized folliculitis, or generalized induration (including induration along the tunnel tract), or bulla(e), or skin tear(s) ≤ 10% CBA, or pain, or discharge, or microbiologically documented CRLI
☐ 4 Exfoliative dermatitis, or ulcerating dermatitis, or ruptured bulla(e), or skin tear(s) > 10% CBA
☐ Not applicable (tandem assessment not done)

1.23 Final CASI grade (if a tandem assessment not done, then enter CASI grade assessment #1):

☐ 0 None
☐ 1 Scattered macular eruption, or scattered papular eruption, or asymptomatic erythema, or scattered pruritus
☐ 2 Scattered macular eruption with pruritus, or scattered papular eruption with pruritus, or erythema with pruritus, or scattered vesicular eruption, or scattered folliculitis, or scattered induration, or maceration, or generalized pruritus, or shiny skin
☐ 3 Generalized macular eruption, generalized papular eruption, or generalized vesicular eruption, or generalized folliculitis, or generalized induration (including induration along the tunnel tract), or bulla(e), or skin tear(s) ≤ 10% CBA, or pain, or discharge, or microbiologically documented CRLI
☐ 4 Exfoliative dermatitis, or ulcerating dermatitis, or ruptured bulla(e), or skin tear(s) > 10% CBA
SECTION 1: SCREENING (BASELINE DATA – PART A) (continued)

1.24 Was eligibility criteria met?

☐ Yes
☐ No

1.25 Date of randomization (i.e. enrollment): __|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|_
SECTION 2: BASELINE DATA – PART B

2.1 Sex:
- Female
- Male
- Other

2.2 Disease (indication for HSCT):
- AML
- ALL
- Lymphoma
- CML
- MDS
- Aplastic anemia
- Other: ________________________________

2.3 Stem cell source:
- PBSC
- Bone marrow
- Cord blood cells

2.4 HLA match:
- 10/10
- 9/10
- 8/10
- Other: _________

2.5 GVHD Status (per NIH Consensus Criteria v. 2015) (i.e. presence of ACTIVE GVHD at screening)
- Yes
- No
Participant Code: [L__L__N]

SECTION 2: BASELINE DATA – PART B (continued)

2.6 GVHD organ involvement (as per NIH Consensus Criteria v. 2015)

☐ Not applicable
☐ Mouth
☐ Skin
☐ Muscle, fascia, joints
☐ Genital
☐ Lung
☐ Gastrointestinal
☐ Liver

2.7 SCST within the past seven days:

☐ Yes
☐ No

2.8 Number of CVAD lumens: [___]

2.9 Date Data Collection Completed: [DD__MMM__YYYY]  Initials: ______
SECTION 3: STUDY FOLLOW-UP VISITS

3.1 Visit number:

☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5  ☐ 6

3.2 Visit missed:  ☐ No (If no, go to 3.4)  ☐ Yes (If yes, go to 3.3)

3.3 Reason for missed visit:

☐ Unable to attend – Visiting home community  ☐ Lack of patient time
☐ Unable to attend – In hospital  ☐ Error
☐ Unable to attend – Other reason: ___  ☐ Other
☐ Unknown

Visit date:

3.4 Ideal date: [__|__|__|__|__|__|__|__]

3.5 Actual date: [__|__|__|__|__|__|__|__]

☐ Not applicable (visit missed)

3.6 CASI grade assessment #1:

☐ 0  None
☐ 1  Scattered macular eruption, or scattered papular eruption, or asymptomatic erythema, or scattered pruritus
☐ 2  Scattered macular eruption with pruritus, or scattered papular eruption with pruritus, or erythema with pruritus, or scattered vesicular eruption, or scattered folliculitis, or scattered induration, or maceration, or generalized pruritus, or shiny skin
☐ 3  Generalized macular eruption, generalized papular eruption, or generalized vesicular eruption, or generalized folliculitis, or generalized induration (including induration along the tunnel tract), or bulla(e), or skin tear(s) ≤ 10% CBA, or pain, or discharge, or microbiologically documented CRLI
☐ 4  Exfoliative dermatitis, or ulcerating dermatitis, or ruptured bulla(e), or skin tear(s) > 10% CBA
☐ CASI assessment #1 not done; reason: ________________________________
SECTION 3: STUDY FOLLOW-UP VISITS (continued)

3.7 CASI grade assessment #2 (i.e. tandem assessment):

☐ 0 None
☐ 1 Scattered macular eruption, or scattered papular eruption, or asymptomatic erythema, or scattered pruritus
☐ 2 Scattered macular eruption with pruritus, or scattered papular eruption with pruritus, or erythema with pruritus, or scattered vesicular eruption, or scattered folliculitis, or scattered induration, or maceration, or generalized pruritus, or shiny skin
☐ 3 Generalized macular eruption, generalized papular eruption, or generalized vesicular eruption, or generalized folliculitis, or generalized induration (including induration along the tunnel tract), or bulla(e), or skin tear(s) ≤ 10% CBA, or pain, or discharge, or microbiologically documented CRLI
☐ 4 Exfoliative dermatitis, or ulcerating dermatitis, or ruptured bulla(e), or skin tear(s) > 10% CBA
☐ Not applicable (tandem assessment not done)

3.8 Final CASI grade (if tandem assessment not done, then enter CASI grade assessment #1):

☐ 0 None
☐ 1 Scattered macular eruption, or scattered papular eruption, or asymptomatic erythema, or scattered pruritus
☐ 2 Scattered macular eruption with pruritus, or scattered papular eruption with pruritus, or erythema with pruritus, or scattered vesicular eruption, or scattered folliculitis, or scattered induration, or maceration, or generalized pruritus, or shiny skin
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☐ 4 Exfoliative dermatitis, or ulcerating dermatitis, or ruptured bulla(e), or skin tear(s) > 10% CBA
☐ Final grade not available; reason: ________________________________
SECTION 3: STUDY FOLLOW-UP VISITS (continued)

WBC results (closest result to visit):

3.9 Total WBC: [___|___|___] x10^9/L

3.10 ANC: [___|___|___] x10^9/L

3.11 Date CBC specimen collected: [___|___|___|___]

3.12 Days of SCST since last visit: [___] Days

3.13 For participants with active skin GVHD at baseline or at previous visit:
   Is skin GVHD still active? □ No □ Yes □ Not applicable

3.14 For participants with NO active skin GVHD at a prior visit:
   Has active skin GVHD occurred since last visit? □ No □ Yes

3.15 Date of relapse: [___|___|___|___]
   □ Not applicable (since last visit)

3.16 Date of death: [___|___|___|___]
   □ Not applicable (since last visit)

3.17 Date Data Collection Completed: [___|___|___|___] Initials: ______
SECTION 4: EPISODES OF FEVER

4.1 Date of temperature $\geq 38^\circ$ Celsius:  

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4.2 Date of temperature $\geq 38^\circ$ Celsius:  

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4.3 Date of temperature $\geq 38^\circ$ Celsius:  

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4.4 Date of temperature $\geq 38^\circ$ Celsius:  

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4.5 □ No episodes of temperature $\geq 38^\circ$ Celsius during study period

4.6 Date Data Collection Completed:  

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Initials: _______
Participant Code: |__|__|__|__|__|__|__|

SECTION 5: EPISODES OF CRBSI CONFIRMED BY DTP

5.1 Date of positive blood culture #1: |__|__|__|__|__|__|__|__|__|__|__|__|
Organism(s) cultured:  5.1.1
5.1.2
5.1.3

5.2 Date of positive blood culture #2: |__|__|__|__|__|__|__|
Organism(s) cultured:  5.2.1
5.2.2
5.2.3

5.3 Date of positive blood culture #3: |__|__|__|__|__|__|__|__|
Organism(s) cultured:  5.3.1
5.3.2
5.3.3

5.4 No episodes of positive blood cultures during study period (choose reason):

☐ No blood cultures drawn during study period OR
☐ Blood cultures drawn during study period were not positive

5.5 Date Data Collection Completed: |__|__|__|__|__|__|__|
Initials: ______
SECTION 6: MICROBIOLOGICALLY CONFIRMED CRLI

6.1 Date of positive exit site culture: [DD MMM YYYY]
Organism(s) cultured: 6.1.1
6.1.2
6.1.3

6.2 Date of positive exit site culture: [DD MMM YYYY]
Organism(s) cultured: 6.2.1
6.2.2
6.2.3

6.3 Date of positive exit site culture: [DD MMM YYYY]
Organism(s) cultured: 6.3.1
6.3.2
6.3.3

6.4 No episodes of positive local cultures during study period (choose reason):

☐ No local specimens collected during study period OR
☐ Local specimens collected during study period were not positive

6.5 Date Data Collection Completed: [DD MMM YYYY] Initials: _____
Participant Code: [___][___][___]  

SECTION 7: HOSPITAL ADMISSION AND DISCHARGE DATES

Hospitalization 1:

7.1.1 Admission date: [___][___][___][___][___][___][___][___]

7.1.2 Discharge date: [___][___][___][___][___][___][___][___]

Hospitalization 2:

7.2.1 Admission date: [___][___][___][___][___][___][___][___]

7.2.2 Discharge date: [___][___][___][___][___][___][___][___]

Hospitalization 3:

7.3.1 Admission date: [___][___][___][___][___][___][___][___]

7.3.2 Discharge date: [___][___][___][___][___][___][___][___]

Hospitalization 4:

7.4.1 Admission date: [___][___][___][___][___][___][___][___]

7.4.2 Discharge date: [___][___][___][___][___][___][___][___]

Hospitalization 5:

7.5.1 Admission date: [___][___][___][___][___][___][___][___]

7.5.2 Discharge date: [___][___][___][___][___][___][___][___]

7.6 ☐ No overnight hospital admissions during study period

7.7 Date Data Collection Completed: [___][___][___][___][___][___][___][___]  

Initials: _______
SECTION 8: UNSCHEDULED DRESSING CHANGES

8.1 Date of unscheduled dressing change: ________________
    DD MMM YYYY

8.2 Date of unscheduled dressing change: ________________
    DD MMM YYYY

8.3 Date of unscheduled dressing change: ________________
    DD MMM YYYY

8.4 Date of unscheduled dressing change: ________________
    DD MMM YYYY

8.5 Date of unscheduled dressing change: ________________
    DD MMM YYYY

8.6 Date of unscheduled dressing change: ________________
    DD MMM YYYY

8.7 Date of unscheduled dressing change: ________________
    DD MMM YYYY

8.8 No unscheduled dressing changes during study period.

8.9 Date Data Collection Completed: ________________
    DD MMM YYYY

Initials: ______
**Participant Code:** [___|___|___]

**SECTION 9: END OF STUDY**

9.1 Date of last study visit: [___|___|___|___|___|___|___|___]

9.2 Reason for last study visit:
- [ ] Early withdrawal – Go to 9.3
- [ ] Participant completed all six study visits – Go to item 9.4

9.3 Reason for early withdrawal:
- [ ] Cuff extrusion
- [ ] Neutropenia for > 7 days
- [ ] Temperature $\geq 38^\circ$ Celsius $>$ 3 consecutive days
- [ ] T-CVAD removal (planned – due to discharge from daycare)
- [ ] T-CVAD removal (unplanned – due to bloodstream infection)
- [ ] T-CVAD removal (unplanned – due to thrombus)
- [ ] T-CVAD removal (unplanned – accidental)
- [ ] T-CVAD removal (unplanned – other reason: ________________)
- [ ] Hospital admission $>$ 14 days
- [ ] Participant died
- [ ] Participant decision
- [ ] Physician decision

9.4 For **no-dressing** participants – Did participant choose to continue with no-dressing post study?

- [ ] Yes
- [ ] No
- [ ] Not applicable (Participant in dressing group)

9.5 **Date Data Collection Completed:** [___|___|___|___|___|___|___|___]  **Initials:** ______
SECTION 10: Summary (Study Endpoints and Descriptive Items)

10.1 Total CASI episodes: | | *Do not count baseline; count a finding of Grade 1, 2, 3 or 4 as one episode
10.2 Highest CASI grade: | | *Do not count baseline; enter highest grade during follow-up period
10.3 Did participant have one or more CASI episodes ≥ grade 2? ☐ Yes ☐ No *Do not count baseline
10.4 Did participant have one or more CRBSI episode(s)? ☐ Yes ☐ No *from randomization to last visit
10.5 Total number of CASI assessments: | | *Do not count baseline
10.6 Total number of CASI episodes grade 0: | | *Do not count baseline
10.7 Total number of CASI episodes grade 1: | | *Do not count baseline
10.8 Total number of CASI episodes grade 2: | | *Do not count baseline
10.9 Total number of CASI episodes grade 3: | | *Do not count baseline
10.10 Total number of CASI episodes grade 4: | | *Do not count baseline
10.11 Total number of dressing changes: | | | | from randomization to last visit
10.12 Total number of unscheduled* dressing changes: | | | | from randomization to last visit
*For “No-Dressing” group: Any dressing change is “unscheduled”.
*For “Dressing” group: A dressing change between “Visit” dates is “unscheduled”
10.13 Total number of hospital admissions: | | | | from randomization to last visit
10.14 Total days SCST: | | | | from randomization to last visit
10.15 Total days active skin GVHD: | | | | from randomization to last visit

Dressing Group only:

10.16 Did participant have CASI at baseline (any grade)? ☐ Yes ☐ No
10.17 Did participant have CASI at final visit (any grade)? ☐ Yes ☐ No

10.18 Date Data Collection Completed: | | | | | | | | | | Initials: _______