Cover letter for Protocol

Official title: Cooling Leg and Foot Ulcer Skin Post Healing to Prevent Ulcer Recurrence (MUSTCOOL)

NCT02626156

Document date: 07/23/2018

Medical University of South Carolina
Protocol

PI Name: **Teresa J. Kelechi, FAAN, RN, PhD.**

Study Title: **Monitoring and managing newly healed chronic leg and foot ulcer skin temperature: a cooling intervention (MUSTCOOL) to prevent ulcer recurrence**

TABLE OF CONTENTS

A. SPECIFIC AIMS

Purpose: Elevated skin temperature after closure of a chronic ulcer is predictive of ulcer recurrence due to aberrant and persistent inflammation resulting in tissue destruction [1-3]. The proposed randomized controlled trial (RCT) will test a patient-directed self-monitoring/self-management intervention (**MUSTCOOL**) with respect to its ability to prevent recurrence of chronic venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs) while improving symptoms, physical activity, and quality of life. This will be achieved by: 1) *m*onitoring newly healed *u*lcer *s*kin *t*emperature with a non-invasive hand-held dermal thermometer; and, 2) modifying the local skin environment (i.e., elevated temperature) by *cool*ing the focal area with a cooling "pack" noted for its anti- inflammatory properties [4-6].

Negative impact of chronic ulcers: Chronic ulcers affect 6.5 million individuals, 5 million of whom have ulcers of the legs and feet related to diabetes, vascular and/or neuropathic disorders. These ulcers represent a substantial portion of the health and cost burden of those chronic illnesses [7-9]. For example, in 2008, the National Institute of General Medicine Sciences reported ~$20 - 25 billion was spent for ulcer care, and this does not account for the costs of human suffering and the negative impact on physical activity and quality of life [10,11]. Dollar and human suffering costs are increased when ulcers become chronic and recalcitrant to treatment. Unfortunately, incidence and prevalence of leg and foot ulcers are expected to increase as a result of the growing aging population suffering with diabetes and obesity [12].

High recurrence rates: VLUs and DLUs show extremely high recurrence rates: 70 – 96% of VLUs recur within 2 to 3 months of healing [13,14] while the five-year cumulative DFU recurrence rate is 66% [15,16]. If even half of these recurrent ulcers could be prevented, $10 billion in savings on expenditures for hospital and outpatient ulcer care would be saved and associated suffering eliminated.

Our prevention intervention: Our prior research supported and refined **MUSTCOOL,** a self-management prevention model for VLUs (Drs. Kelechi & King) and DFUs (Drs. Bharara & Shibuya)[2,3,17-19]. This collaborative team will extend **MUSTCOOL's** ulcer prediction (monitor for elevated skin temperature) and prevention (cooling pack therapy) intervention by determining if prophylactically cooling previously ulcerated skin due to a chronic VLU or DFU three times weekly during the immediate and intermediate post healing remodeling phase (closure to 6 months) will prevent ulcer recurrence, reduce pain, enhance physical activity, and improve quality of life. Specifically, for a skin temperature increase 2°F above baseline for two days in a row, a bolus dose of cooling for 5 consecutive days will be implemented.

Enhancements to intervention: For this RCT, we have made several technical and methodological refinements to **MUSTCOOL**. First, we will use an extremely low cost infrared camera to map temperature gradients of the healed leg and foot skin to identify any "hot spot(s)" which will visualize overall tissue health and will be monitored by participants using the thermometer. Second, a user-friendly cooling pack (local cooling) will be used instead of the cuff (regional cooling) based on acceptability data from our ongoing RO1 study participants. Third, we will quantitatively measure physical activity using state of the art accelerometry. Finally, we will test a new data-driven temperature-monitoring schedule, targeting the skin of newly healed chronic ulcers that took longer than 12 weeks to heal. In 180 patients with a newly healed chronic ulcer, 90 patients will be randomized to receive the experimental cooling pack + standard of care (compression, elevation or footwear) or control placebo pack + standard of care to apply to the affected "hot spot" in the presence of elevated skin temperature. Randomization will be stratified by ulcer type, VLU versus DFU (n=90 in each group). During the 6-month study period, this trial aims to:

1. **Test the MUSTCOOL intervention (cooling pack) compared to control group (placebo pack) on: outcome of incidence of ulcer recurrence; and, impact on pain, physical activity and quality of life.**

2. ***Assess the implementation self-management process measures including: a) appropriate use of thermometer, b) application of pack to the "hot spot" for 5 consecutive days for 30 minutes (fidelity to self-management), c) utilization of supportive reinforcement, d) reactions/satisfaction of participants, and e) staff ratings and perceptions for replicability.***

Impact: Our preliminary data suggest significant improvements in health outcomes: a reduction in leg ulcer development, improved pain, and higher quality of life. However, analysis of monthly data from our ongoing RO1 has found a non-sustained reduction in skin temperature during 30 days of a 30-minute daily initial cooling dose. Thus we have modified **MUSTCOOL's** cooling delivery to be based on skin temperature elevation above an individual's baseline and have participants prophylactically cool the affected skin at home under real-life conditions.

B. BACKGROUND AND SIGNIFICANCE

This study addresses morbidity and quality of life issues with a very challenging population with chronic ulcers. It addresses an RFA priority, the purpose of which is to test a self-monitoring/management strategy that can be implemented in community settings, chiefly the home. **Chronic ulcers cause pain and suffering, negatively affecting physical activity and quality of life**. Populations with chronic ulcers, such as individuals with chronic venous disease, and/or diabetes and/or neuropathy have major life-style issues. They are often obese and plagued with multiple co-morbid conditions such as hypertension and arthritis. Many have experienced multiple ulcers in their lifetimes that take months, even years to heal. Additionally they are physically inactive leading to significant mobility problems [11]. Chronic ulcer patients who are physically inactive suffer disproportionately; many experience prolonged ulcer healing and other complications such as amputations [16]. They are physically de-conditioned, some able to take only a few steps at a time, are much less active, have poor balance, slower walkers, and experience pain [20,21]. Our MUSTCOOL leg and foot ulcer prevention intervention, while a self-care approach, may be viewed by these patients as a means by which their physical activity and quality of life could be improved. Unfortunately they are poor candidates for surgical or pharmacologic intervention due the severity of the disease process or co- morbidities, or they have failed these therapies in the past.

C. PRELIMINARY STUDIES

We have conducted and published preliminary work in the area of pain and physical activity. *First*, we developed a **c**onditioning **a**ctivities for **l**ower **l**eg **f**unction (CALF) intervention combined with a behavioral component, **m**otivational **e**nhancement communication (MECALF), delivered by wound care clinic providers to leg ulcer patients. It was found to be feasible and acceptable by both patients and providers [22]. Signals of significance were found in leg function, in particular in pain reduction ($p = 0.04$) in the lower legs of leg and foot ulcer patients over the course of the six-week study compared to patients who received an exercise handout only. *Secondly,* in another study, the CALF intervention was delivered by a exercise sciences coach through online face-to-face Internet sessions via Skype® and demonstrated statistically significant improvements in ankle dorsiflexion and leg strength (both $p = 0.03$) [23]. Patients had a history of leg ulcers and participated in three daily doses of CALF. The face-to-face Internet interactions were feasible, even for patients who lived in subsidized housing. While the goal of this study was to test the feasibility of the physical activity program, we observed a very high level of patient satisfaction with being able to initiate contact with the coach via Skype® and signals of efficacy in improvement in function even with small daily doses. *Finally,* in a recent randomized study evaluating the effectiveness of two offloading modalities for diabetic foot ulcer healing we demonstrated the need for objective physical activity assessment (Dr. Bharara, manuscript in progress). Our data suggest while walking may delay healing, unprotected standing may be an even more unrealized and sinister culprit for

chronic non-healing ulcers and recurring ulcers in individuals with diabetes.

The remodeling phase of healing (final repair process) of chronic ulcers is prolonged, has inflammatory components, and elevated skin temperature. Healing normally proceeds through four programmed stages: hemostasis, inflammation, proliferation, and remodeling. The remodeling phase overlaps with other phases of wound healing and is highly regulated by growth factors and cytokines secreted by inflammatory cells [24]. In acute wounds, wound healing progress requires precise integration of multiple physiology events including cell migration, cell infiltration, cell proliferation, and extracellular matrix (ECM) deposition [25]. In chronic non-healing ulcers, however, defective remodeling of the extracellular matrix due to prolonged inflammation is observed [25]. Factors intrinsic to underlying metabolic disease, such as diabetic hyperglycemia, or increased hydrostatic pressure associated with venous disease, can enhance and perpetuate the inflammatory response [26]. Studies have shown differences in cellular infiltration and extracellular matrix composition of chronic diabetic and venous ulcers versus acute wounds [27]. These non-healing wounds fail to progress through the normal phases of wound repair, instead, they remain in a chronic inflammatory state characterized by abundant neutrophil infiltration and elevated pro-inflammatory cytokines such as TGF-b, IL- 1, IL-6, and TNF-α [26,27]. Furthermore, studies in diabetic transgenic mice also indicate that prolonged persistence of neutrophils and macrophages during the late phase of repair impairs wound healing [28]. The persistence of inflammatory cells promotes an inflammatory environment and stimulates the production of tissue-degrading proteinases [29]. It has been hypothesized in many studies that such an excessive or prolonged inflammatory response results in increased tissue injury and that an unbalanced inflammatory response may continue after the tissue has closed [30-33]. This is particularly notable in chronic ulcers after closure [34-36] as evidenced by persistently elevated skin temperature [37]. Drs. Bharara's and Kelechi's science underpins this proposed study by suggesting that detecting inflammation in the foot [2,17] and leg [38] in "remission" could provide insights into the remodeling phase of ulcer healing. **Preliminary work:** Our science has advanced the field by providing a mechanism by which persistently elevated skin temperature is measureable and predictive of ulceration. This proposed study builds on the landmark research of skin temperature elevation's measurement suitability in predicting diabetic/neuropathic foot ulcers after healing in high-risk patients [1,39-41]. Dr. Kelechi has demonstrated temperature elevation in lower leg skin inflamed by venous disease is as equally predictive [3,42]. Drs. Bharara and Shibuya continue to advance the field in diabetic foot ulcer populations by exploring new infrared and physical activity monitoring technology and cryotherapeutic modalities. Taken together, our work in the field over the past 10 years has evolved a model of ulcer prediction based on self monitoring of skin temperature using infrared thermometers [2,43] as ulcers progress through the remodeling phase. Our team and others have demonstrated that infrared and thermal technologies are well established as validated and reliable instruments to measure skin temperature of chronically inflamed skin [44-50] and skin affected by other conditions, such as neuropathy [51,52].

1.1. Cooling (cryotherapy) reduces tissue metabolism and prevents tissue destruction, thus has the potential to prevent leg and foot ulcer recurrence. While the specific physiological mechanisms associated with cooling chronically inflamed skin are poorly understood, cooling causes an initial vasoconstriction in skin blood vessels, which results in decreased local blood flow to the area. Cooling also prevents localized fluid leakage from the microcirculation and thus reduces inflammation (i.e., edema, redness, eczema). Used for centuries as a treatment modality for musculoskeletal injuries and acute inflammatory conditions [53] cryotherapy reduces the metabolic rate of tissue, and impedes the destruction of otherwise uninjured adjacent tissue by limiting injury [54]. It has been shown to prevent diabetic foot ulcers from becoming inflamed [55]. Skin heats up before it breaks down (skin temperature is increased by approximately 1.8□C in venous-affected skin and spikes prior to ulceration) [38], and

prophylactically cooling a focal or localized area of affected skin reduces the risk of skin changes and ulceration by reducing microcirculatory blood flow, vessel permeability and tissue metabolism [55]. **Preliminary work.** The preliminary findings from our cryotherapy R21 suggested a signal of efficacy in reducing tissue metabolism (blood flow), pain reduction and ulcer prevention [19]. Cooling the skin significantly reduced blood flow on average by 6 perfusion units (PU), from 15 to 9 PU (normal is 3 – 5 PU) after four weeks of cooling [18]. We also found that vasoconstriction and reduced blood flow can persist for greater than one hour after removal of cryotherapy, even in the presence of skin rewarming at room air [56]. We developed this proposed study's protocol based on principles of heat transfer, microcirculatory thermoregulation, studies of cryotherapy and healthy skin, and pathophysiologic mechanisms of venous disorders, supplemented with consultation with Dr. Shibuya, and additional preliminary work conducted post R21.In regards to pain, cryotherapy offers an analgesic effect that can be realized within 3 minutes by locally destimulating pain receptors, which are located in the subcutaneous tissue [57,58]. These findings led to the currently funded R01 to test the efficacy of a sequenced cooling regimen over a 9-month period for patients with venous disease, damaged skin and/or a history of healed venous ulcers. The ongoing study is evaluating efficacy on pain, ulcer occurrence and quality of life (in year 4). While we are in the last year of the study and will analyze data to determine outcomes on ulcer prevention, first month data (§Figure 1) suggest that an initial acute daily cooling regimen, compared to a placebo, demonstrated a clinically, but no statistically significant difference in skin temperatures measured daily (cyrotherapy cuff treatment + leg elevation versus placebo cuff + leg elevation.) There was a non-significant trend towards lower skin temperatures in both groups. These findings suggest that an acute cooling period is unnecessary and that a reduced frequency (three times weekly for 30 minutes based on our preliminary data) could be adequate as a maintenance dose to keep the skin temperature "in check". These findings are further supported by Dr. Bharara's inflammation proof of concept work in diabetes [59] and Dr. Shibuya's post-operative cryotherapy research [60].

Figure 1: Month 1 daily cooling data

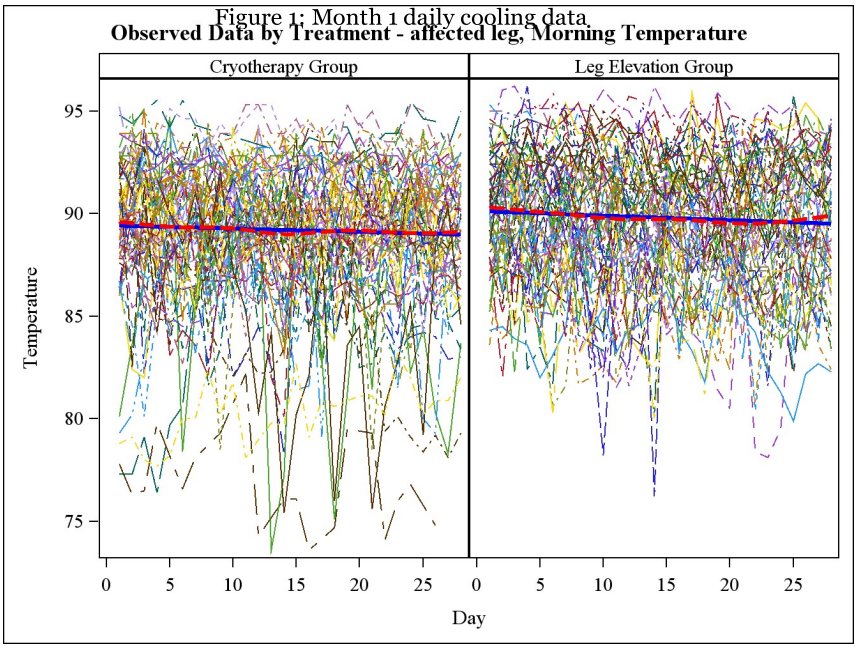

Figure 1.

Summary: This trial is significant due to the burden of chronic ulcers, the complex physical

characteristics of the population, and need to reach them with a supportive strategy. We hypothesize that this novel model will significantly improve the health and quality of life of these patients, and that the intervention will become a feasible standard of care, activating patients to be better self-care managers. We want to develop this self- management cooling approach as an evidence-based practice guideline and as such, this

D. RESEARCH DESIGN AND METHODS (including data analysis)

D.1. Study overview

This six-month randomized controlled trial will use a two-group longitudinal design to test MUSTCOOL home- based self-monitoring and self-management ulcer prevention intervention for patients at high risk of leg and foot ulcer recurrence. The study targets individuals with newly healed chronic VLUs and DFUs that took longer than 12 weeks to heal. For aim 1, real time physical activity monitoring using an accelerometer, self-monitoring of skin temperature using infrared thermometry, and self-management of newly healed skin using a small cooling pack or placebo pack to maintain the skin environment will be studied for reduced ulcer recurrence rates, pain, physical activity and quality of life. We will test the intervention on 180 patients with newly healed leg and foot ulcers randomized to receive the experimental cooling pack or control placebo pack. The design incorporates methods that maximize reproducibility, control bias and transparency of reporting, as noted in Aim 2. Table 1 summarizes the changes in protocol from our preliminary work to the current study.

D.2 Interdisciplinary team

Our interdisciplinary team includes Dr. Kelechi, PhD, RN a nurse scientist and practicing certified wound care nurse. She will lead the team as principal investigator. She has extensive expertise in managing clinical trials for populations with chronic venous disease, using infrared technology, and cryotherapy and physical activity interventions. Her clinic population includes patients with chronic venous and diabetic foot ulcers. Dr. Bharara, PhD, is a bioengineer with expertise in infrared and cooling technologies and their application to patients with diabetic foot ulcers. He also has expertise in using objective biomechanical assessment instruments that will be used in the study to assess physical activity. Dr. Shibuya, DPM, is a podiatric surgeon with expertise in cryotherapy and its application to patients with diabetic foot ulcers. He is presently serving as the cryotherapy consultant on Dr. Kelechi's ongoing R01. Drs. Bharara and Shibuya bring extensive expertise in diabetic foot ulcers and will guide the study procedures related to this population. Dr. King, MD has provided medical oversight on all of Dr. Kelechi's previous studies, has extensive experience with chronic populations, and expertise in clinical trials and risk/safety monitoring. Dr. King is currently serving as the chair of our R01 and R21 (palliative wound care intervention study) DSMB. We will develop our DSMP under Dr. King's watchful guidance. Dr. Mueller, PhD, who has expertise with managing R01 level NIH RCTs, and who has provided biostatistical support for Dr. Kelechi for the past 8 years, will provide statistical expertise and coordinate data analyses.

D.3 Setting, eligibility, recruitment and enrollment

TABLE 1: REFINEMENTS THAT INFORMED NEW MUSTCOOL INTERVENTION

	Old	***New***	***Rationale***
Cooling device	Regional cooling: Cuff encircled lower leg or foot	Local cooling: Pack that comes in three sizes, 3X3, 5X5, 10X10 with net tubing to anchor to foot or leg	User complaints: cuff too heavy, made pt. feel cold all over: will cool affected area "hot spot" only (unpublished R01 exit data)[19]

Thermometer	Contact thermometer without memory	Non-contact thermometer with laser pointer and 100 reading memory	Reduced burden on patient to record temperatures (60% of patients make errors in recording)
Skin site (affected area "hot spot")	VLU: 5 cm above medial malleolus; DFU, site of previous ulcer	VLU: Infrared image of ant./lat./med/ gaitor area: DFU: plantar surface of foot	Identify the "hot spot" with thermography that will be targeted for home monitoring [2]
Baseline temperature	No baselines were established for VLU or DFU "hot spots"	Baseline will be established by averaging the first 30 daily morning temperatures	Our R01 data of morning leg temperatures showed no statistically significant variation among temperatures taken 12 hours after treatment for 30 days [19]
Frequency of temperature monitoring	VLU: Before and after cooling and 12 hours later (morning); DFU, daily (no specific time recommended)	Morning only	Standardized for this study; reduced effects of footwear and ambulation that could potential increase surface temperature on plantar region of foot [61]
Skin temperature target	Cool if 4°F (2.2°C) above baseline	Cool if 2°F above baseline	By the time the tissue reaches 4°F, there is significant inflammation and tissue destruction [41]
Population	Any VLU or DFU patient regardless of length of time to healing	Only those with previously healed chronic ulcers (≥ 12 weeks to heal)	Focus of RFA is on chronic ulcers; the emphasis for this study is prevention

D.4 Setting: The study will recruit participants from 5 major wound care centers and specialty practices (§ letters of support) within a 75-mile radius of Charleston, SC, as well as from one located in Greenville, NC. These centers and practices serve a large proportion of urban and rural residing, racially and ethnically diverse patients with leg and foot ulcers. The study will be conducted at the Research Nexus (CTSA) on the campus of the Medical University of South Carolina, at the Spartanburg Regional Healthcare System's Wound Healing Center, and at East Carolina University, NC.

D.5 Sample eligibility criteria: English speaking adults age 18 years-of-age or older with a healed VLU or DFU will be invited to participate (§Table 2).

TABLE 2: INCLUSION & EXCLUSION CRITERIA	
Inclusion for enrollment	***Exclusion***
Newly healed leg or diabetic foot ulcer within past six weeks	Open leg or foot ulcers
Ankle brachial index 0.8- 1.3mmHg (rule out absence of arterial disease)	Cognitive impairment: unable to recall 2 or more words or draw clock Mini-Cog™ (0.84) for cognitive impairment [62]
Willing to wear compression stockings and appropriate footwear	Chronic inflammatory or vascular conditions where blood flow of skin may be impaired such as Lupus erythematosus, Raynaud's, scleroderma, chronic regional pain syndrome, multiple sclerosis, hypersensitivity to cold, on chemotherapy
Working freezer	Unable to preform required protocol activities without assistance (return demonstration to study staff)
Willing to travel for study visits	

D.6 Recruitment and retention plan:

We have developed an extensive recruitment plan for our previous studies and have refined several strategies to ensure enrollment targets are met for this study. Based on our recruitment metrics from our ongoing R01 and Dr. Kelechi's experience as the director of recruitment of MUSCs CTSA, we expect to enroll 1 subject for every 5 approached and screened (#1 reason for not enrolling is an abnormal ankle brachial index). The goal is to enroll ~6 subjects per month for 3 1/2 years, accounting for an expected attrition rate of ~25% (nature of the chronically-ill population with frequent hospital admissions). Our recruitment plan includes referrals from centers and practices (25% of subjects will be referred). However we anticipate using other recruitment methods that we have found particularly successful including television, radio and billboard advertisements, use of our CTSA's SCResearch.org website, and our community based participatory research advisory groups. At MUSC, a chart review will be conducted for the identification of potentially eligible patients per the study inclusion/exclusion criteria and recruitment purposes. Potentially eligible patients, that have agreed to be contacted for future research by logging their MUSC Research Permissoins preference in MyChart will be contacted by phone and invited to participate in the study. All other identified patients will be initially approached and contacted through their provider about the study, if the provider feels the study is appropriate. Additionally, we will create an online REDCap survey that will be accessible through a PI designated research web-page (https://www.musc.edu/nursing/initiatives/researchoffice/currently_active_studies.htm) on MUSC secure servers that will allow potentially eligible individuals to self-prescreen through yes/no questioning and have the researchers contact them should they elect to do so. We have budgeted for these strategies accordingly, based on our current experience with our ongoing R01. There is a need to incentivize center and practice referrals and to that end, we will provide $20 for every enrolled participant in the form of a "credit" gift card that can be used for whatever purposes deemed appropriate by the practice. We also have implemented a very successful contingency management approach for retention at one of our study sites (a drawing from a fish bowl at each visit with the opportunity to win from $1 to $100). The attrition rate for this site is ~17% compared to 30% (average of other sites' attrition rates). We will include this same strategy in the proposal study.

D.7 Randomization, masking and allocation concealment: A permuted block randomization strategy developed by Dr. Mueller will be used to assign newly healed VLU and DFU patients to treatment or placebo. Randomization will be stratified by type of ulcer, VLU or DFU. The research assistants, PI and consultants will be blinded (masked) to treatment assignment. To minimize the likelihood that the mask will be broken, e.g., the next treatment assignment can be guessed, the block size will be varied. At baseline, a research assistant will consent, determine eligibility, enroll, collect baseline data, (i.e., demographics, physical activity, pain and quality of life), instruct participants on treatment procedures and provide all study supplies, except for the pack. Both groups will receive identical instructions via a 3-minute videotape shown during the baseline visit. They will complete a 5-item verbal test to demonstrate understanding of procedures. To ensure allocation concealment, after the participant has been successfully instructed on the protocol (100% passing on test), another researcher will randomize participants within the study REDCap database to receive the cooling pack treatment or placebo, and will give the appropriate pack to the participants. Researchers conducting study visits, collecting measures and performing data entry will remain blinded to treatment during return visits 1 – 4.

D.8 Sample size determination including clear justification and power analysis.
The primary efficacy outcome for sample size calculation for this study is recurrence of at least one venous or diabetic ulcer over the study period. Based on a two group continuity corrected Chi-square test

of equal proportions, with 90 subjects per group we will have >90% power to detect a difference in proportions with an odds ratio for recurrence of VLU/DFU of 3.0, assuming 25% of subjects experiencing a recurrent ulcer in the cooling group compared to 25% in the placebo group, □□= 0.05 (Type I error rate), two-sided test. To account for drop-out immediately after randomization, and the dilution effect of intent-to-treat (ITT) analysis, we inflate the sample size by 25% to obtain a final sample size of 120 subjects randomized to each group (N=240) for ITT analysis. For the analysis of continuous efficacy outcome measures (change from baseline in quality of life and pain) we will have 85% power to detect a difference of 0.45 s between the groups assuming □□= 0.05 (Type I error rate), two sided; independent sample t-test comparison of means; equality of variance between groups. Based on our previous pilot study comparing gel-cooling to leg elevation short term this effect size is equivalent of a raw effect size of 1.3 units on the VEINES Quality of Life scale (assuming s=2.8) and a raw effect size of 1.1 units on the visual analog pain scale (assuming s=2.5).

D.9 Protocol

Aim 1: Test the MUSTCOOL intervention (cooling pack) compared to control group (placebo pack) on: outcome of incidence of ulcer recurrence; and, impact on pain, physical activity and quality of life.

Intervention components – The self-monitoring and self-management strategies in the MUSTCOOL intervention are identical for both groups. The only difference is the material composition used in the placebo is developed from cotton. Participants will agree to standard of care: VLU will wear compression stockings and DFU will wear diabetic footwear.

Pre-intervention temperature mapping of lower leg and foot "hot spots". After participants are enrolled, the skin site of the recently healed VLU or DLU will be imaged (photographed) with an infrared camera (Scout® by WoundVision LLC, Indianapolis, IN) by study personnel. These thermal images and participant data (including: subject ID#, skin thermal characteristics, and study visit date) will be instantaneously uploaded via the internet and stored on WoundVision's HIPAA compliant secure servers. Images will be taken at baseline, months 1, 3 and 6. The "hot spot" or area that has the highest temperature reading will be marked with a dermal ink pen, the site where participants will take daily skin temperatures at home. They will be instructed to remark the same spot each day or after bathing/showering. We will track whether the marked "hot spots" have changed in size or location. Camera software analyzes % change in Benchmarks for success: surface area that will be compared at each study visit. The affected skin of the cooling patch group, compared to the placebo, will have smaller and fewer "hot spots" at each visit and at the end of the study.

In accordance with HHS OHRP Guidance on Engagement of Institutions in Human Subject Research B(7) (http://www.hhs.gov/ohrp/policy/engage08.html) WoundVision will not be considered engaged in human subject research as they will be unable to readily ascertain the identity of participants from the data they will be hosting (subject ID#, skin thermal characteristics, and study visit date) from each of the participating sites. WoundVision will not have access to any keys that link subject names and/or address, telephone numbers etc. to their study ID#. MUSC and WoundVision LLC will enter in a service agreement for the provision of data hosting services and protection of data confidentiality. At the end of the study WoundVision will provide the MUSC researchers with a copy of all study data, and delete all hosted study data from their HIPAA compliant secure servers.

Self-monitoring with infrared thermometer. Participants in both groups will be instructed to self-monitor the marked "hot spot" daily prior to getting out of bed in the morning with a non-contact infrared thermometer (IRT730K, General Tools & Instruments, NY, NY) (§Table 2). The thermometer has a laser pointer that targets the marked area and automatically stores the last 100 readings for recall. The handle of the thermometer has a "trigger" that when pulled, emits a laser beam at the marked spot and when released, records the temperature. The thermometer will be programmed at the second visit to automatically sound an

alarm when the temperature rises 2°F above the mean temperature. The mean will be calculated by the research assistant at visit 1 by averaging the first 30 daily readings. While the thermometer date and time stamps each reading, we will ask participants to record the daily readings on a paper log given to them on a clipboard with an attached pen at the start of the study. This "back up" log will be available in the event of a mechanical error with the thermometer. It is also a reliability/validity measure of participant self-report which may be important to future dissemination studies.

Self-management with cooling pack – Participants in both groups will apply the pack (cooling or placebo) at a consistent time each day (e.g. 7 PM) to the affected leg or foot skin "hot spot", both prophylactically (maintenance) and preventatively (bolus dosing) (§Table 2). The rationale for using cooling packs compared to cuffs or wraps is based on exit interview comments from participant experiences in our ongoing cyrotherapy R01 in which a lower leg cooling cuff (regional cooling of the lower leg) was used. Some of the user comments include: "I felt cold all over when using the cuff", "why do we need to cool so much skin when it's just that one area that has the problem?", "that cuff was too heavy and weighed down my leg", and "the nurse worked so hard to make it fit but it didn't feel right on my leg". In response, the proposed study will use readily available small packs, applied only locally (versus regionally) to the "hot spot" on the leg or foot (§Table 3 for refinements to study protocol). The topical cooling pack (Therapy Pack, Elastogel, Southwest Technologies, Kansas City, MO) to be used in the cooling treatment group is a flexible glycerin-based sheet hydrogel that does not freeze to a solid state and is available in various sizes. We have conducted extensive safety testing of the material prior to our previously conducted R21 and have had no adverse events (e.g., skin injury) reported during the R21 and the ongoing cryotherapy R01. The placebo pack has a cotton filing (manufactured by same company and used in our ongoing R01). Both packs have the same feel and look and are covered with a protective polyethylene covering that can be laundered. Both packs will be stored in the freezer (will give subjects freezer thermometers to make sure freezer temperature is maintained at 0°F) and will be applied to the affected site only. Once removed from the freezer, the placebo pack warms to room temperature within 2 minutes. The packs will be anchored with a tubular retainer that is an expandable elastic latex-free net. Participants will record the date and times they apply the packs to the skin (three times each week for maintenance and 5 consecutive days for bolus dosing) on the "back up" log.

TABLE 3: SELF MONITORING & MANAGING SIX- MONTH DOSING REGIMEN FOR BOTH GROUPS

Monitoring Measure skin temperature of "hot spot" with infrared thermometer	Daily each morning	Temperature date and time stamped in thermometer
Management dosing	***Maintenance***	***Bolus***
Apply experimental cooling or control placebo pack to "hot spot" on lower leg or plantar surface of foot; anchor with retention net	3 X/ week for 30 minutes at a consistent time of day	Daily for 5 consecutive days at a consistent time of day

There are two approaches to the self-management strategy (§Table 3):

Maintenance prophylactic dosing: Participants in both groups will be instructed to apply the pack to the affected skin site of the previously healed ulcer three times each week for 30 minutes with both legs elevated on pillows (we will show the proper height during participant instruction). In preliminary data analysis from our ongoing R01, this dosing regimen has been found to be safe and acceptable. We cannot fully analyze our R01 data to determine outcomes on ulcer prevention until the study is completed.

Bolus preventative dosing: If the temperature is 2°F above the mean temperature, calculated as the average of the first 30 days of cooling, for 2 consecutive days, an alarm will sound from the thermometer, and participants in both groups will be instructed to initiate the bolus cooling dose for 30 minutes over 5 consecutive days. They will resume the maintenance cooling 3 days later.

Benchmarks for success: The cooling pack group compared to the placebo will required fewer preventative bolus dosages over the course of the 6-month study.

Participant instructions: We will develop a 3-minute YouTube video and DVD of study procedures (self monitoring, self management) that will be shown to participants during the baseline visit in order to standardize the instruction. This technique was rated as highly useful by participants in our ongoing cryotherapy R01. An example of instructions includes showing how the pack should be applied directly to the leg or foot affected skin, anchored with retention net, while reclining in a recumbent position with both legs elevated. The flow of information for both groups is as follows:

- Wear the compression stockings and/or diabetic footwear during the day.
- Measure skin temperature of marked "hot spot" with the infrared thermometer each morning before getting out of bed to control for the effects of diurnal patterns, eating, drinking caffeinated or alcohol-containing beverages, and exercise, which influence skin temperature during the day. Thermometer, "back up" log sheet and clipboard with pen will be provided.
- Apply the pack (cooling or placebo) to the lower leg or foot skin and anchor with stretchy net at a consistent time each day (e.g., 7 PM). Participants in the control group will be instructed to remove the pack from the freezer and use after it has been exposed to room air for 2 minutes. The pack material (cotton) is unable to retain the cold.
- Lie supine in the bed or couch with legs elevated 10 inches on pillows during the 30-minute treatment, three times each week. Timer will be provided. Participants who have difficulty with the supine position may use the reclining position and if possible, use pillows to raise the feet.
- After the treatment, participants will place packs in accompanying plastic storage bag and return to the freezer. Freezer temperature should be set at 0°C, the industry standard. All participants will receive a freezer thermometer to make sure temperatures are kept at 0°C. If returning the pack to the freezer immediately after cooling the leg or foot is difficult for participants who prefer to do the procedure in the bed, they can replace the pack the next morning without affecting its temperature, which requires 4 hours in the freezer to achieve maximum coldness. Freezer thermometer will be provided.
- If bolus preventative cooling dose is required, participants will do the treatment (cooling and placebo) for 5 consecutive days, and record dates on "back up" log.
- Re-mark the skin site with the dermal pen (provided) after bathing or showering.
- Wear wrist accelerometer each day during waking hours to monitor physical activity.

Benchmarks for success: Both groups will score 100% correct on the 5-item post-test administered after the instruction.

Outcome measures for Aim 1:

Incidence of leg ulcers - we will track any ulcers that develop during the course of the study using supportive phone calls, logs and participant reports during return visits at months 1, 3 and 6. These data will be entered into REDCap. During month 1, supportive phone calls will be made weekly and then monthly by research assistants, who will inquire about new ulcer development. Leg and foot skin will be assessed during each visit. Participants will be instructed to call the research assistant in the event an

ulcer develops, at which time the participant will be withdrawn from the study. The effect of cooling on ulcers is unknown and could pose a safety risk.

Benchmarks for success: Although it is difficult to precisely predict the effect of cooling on ulcer incidence during the study in these two groups, we view a 50% reduction in the incidence of a leg ulcer in the cooling pack group compared to placebo [7,9].

Impact on pain, physical activity and quality of life – pain will be assessed using a visual analog scale (0.99 interrater reliability) [63] and the Brief Pain Inventory (Cronbach's 0.88) [64], physical activity with an accelerometer (Basis Smart Watch, Basis Science, Inc., San Francisco), a user-friendly activity monitor http://www.mybasis.com/and International Physical Activity Questionnaire (IPAQ) (pooled Spearman R 0.81) [65], and quality of life with the VEINES QOL/sym Questionnaire (internal consistency 0.87; test-retest reliability 0.86) [66], the Neuropathic Pain Questionnaire (NPQ) (internal consistency 0.82), the Geriatric Depression Scale, and the SF-12 Health Survey. The VEINES will be administered to the VLU participant population and the NPQ to the DFU participant population. While we recognize that wrist monitors may not be the most accurate in terms of energy expenditure, we are working with an atypical population where hip or bicep-type accelerometer sensors found in (i.e.,Bodymedia Fit, and Fitbit Zip), may not be feasible. Thus, we have selected a wrist accelerometer based on data that suggest this design may be better suited for chronic populations; results revealed acceptable agreement between the Basis watch and indirect calorimetry found in hip sensors [67]. Basis captures resting movements, is less easy to misplace/lose than hip accelerometers, has multiple-sized wrist bands, and numerous programmability options. These three outcomes will be assessed at baseline, and months 1, 3 and 6. Benchmarks for success: Compared to the placebo group, the cooling pack group will have lower pain scores (lower VAS and IPAQ scores), increased physical activity (e.g., more steps taken and participates more frequently in activities, and higher ratings on the SF-12), and improved quality of life (higher ratings on VEINES or NPQ, and GDS).

Analysis plan for Aim 1

The primary efficacy outcomes are recurrence of ulcers, both venous leg ulcers and diabetic foot ulcers, since enrollment into the study (categorical), and changes in pain, quality of life and physical activity from baseline to the three subsequent visits at 1, 3, and 6 months post-baseline (continuous). In primary analysis we will compare differences in proportions of participants developing a VLU/DFU over the entire study period between the cooling pack and placebo groups using chi-square analysis. We will obtain odds ratios for the categorical outcome measure recurrence of VLU/DFU adjusted for putative covariables such as demographic (age, gender, race/ethnicity, marital status, job category and area of residence) and clinical (time since last ulcer, and wearing compression stockings or footwear [yes/no]) characteristics using logistic regression modeling (LRM). Modeling will be carried out in a sequential fashion. For example a first model will contain recurrence of VLU/DFU (yes/no) as response variable, treatment (cooling vs, placebo) as primary variable of interest and time since last ulcer as adjustment variable. The model will be further adjusted using sets of putative predictive covariables such as demographic and clinical characteristics as well as secondary outcomes pain, quality of life and physical activity (step counts). We will examine effect modifications of covariables through inclusion of a covariable-by-treatment interaction term in the multivariable models. Analyses will be repeated within the ulcer subgroups (VLU and DFU) as appropriate.

Survival distributions for recurrence of VLU/DFU will be obtained for each group using the Kaplan-Meier

product limit method, and will be compared using the logrank test [63, 64, 65]. Cox proportional hazards regression modeling (PHM) will be used with time since last ulcer to recurrence of new ulcer as the dependent variable and treatment (cooling vs. placebo) as the primary independent variable. Additional covariables and interaction terms will be added as described above for LRM analyses.

In analysis of the continuous efficacy outcome measures, we will compare unadjusted mean differences in pain and quality of life total scores from baseline to 1, 3 and 6 months via paired t-tests (or equivalently non- parametric Wilcoxon Signed-rank test) between the (cooling vs. placebo) groups. We will use a general linear models (GLM) approach to compare mean differences for the change from baseline outcome measures adjusted for putative predictive covariables. Modeling will be carried out in a sequential fashion for each outcome variable individually analogous to the modeling described above. Using quality of life as example, the first model will contain change in quality of life from baseline to 6 months as response variable, treatment (cooling vs. placebo) as primary variable of interest and baseline quality of life as adjustment variable. This procedure will be repeated for pain measures as well as the accelerometer step counts/physical activities. For the accelerometer, baseline will be established by averaging the first 30 daily step counts/activities; change from baseline will be assessed at 6 months as described above.

In additional analyses, to examine pain (or analogous quality of life and step counts) change over time, the longitudinal profile of pain (quality of life, step counts) will be compared over the active treatment period using mixed effects models (MEM) analyses. These analyses will estimate the average change in pain (quality of life, step counts) within each group (cooling vs. placebo) and individual change in pain (quality of life, step counts) for each participant. MEM analyses allow for missing data, measurement of study subjects at different time points during the study, and time varying covariates. MEM can also take into account the effect of clustering, i.e. correlation of repeated pain (quality of life, step counts) measurements within one subject. The efficacy variable pain (quality of life, step counts) will be used as the dependent variable with treatment status (cooling vs. placebo), time (visit) and time-by-treatment interaction as primary independent variables. In a second step, additional covariables will be included in the models to adjust for putative predictive variables such as demographic and clinical characteristics as well as secondary outcomes as appropriate. Effect modifications of covariables will be examined through inclusion of a covariable-by-treatment interaction term in the multivariable models. MEM methods (e.g., generalized linear mixed models, GLMM) for binary, count, or ordinal outcomes will be applied where appropriate. Further, we will determine frequency distributions of adverse events (AEs) and serious adverse events (SAEs for the two groups and compare proportions within categories of AEs for cooling vs. placebo via chi-square analyses.

Methods for handling missing data:

The research staff will make every attempt to keep participants in the study and to obtain required measurements in order to ensure the completeness of the study data. If study visits are missed to minimize potential bias due to missing observations, participants will be contacted by phone and reasons for missing data will be carefully documented. Participation will only be terminated due to developing of an ulcer (we will continue to monitor via phone calls), safety reasons, withdrawal of consent, or loss to follow-up. Several approaches to handle missing data in the ITT analysis set will be employed. For the primary categorical outcome recurrence of venous leg or diabetic foot ulcer every attempt will be made to obtain information from participants who dropped from the study. If a participant's status for recurrence of VLU/DFU's cannot be established we will carry out sensitivity analysis, i.e. assign "developed a VLU/DFU" to all participants with missing information (worst case) and compare the results of this

analysis to the complete analysis (including only participants with complete information for the primary outcome variable). For continuous variables using a single end-of-study value (e.g. change from baseline), multiple imputation methods will be used. For analyses of longitudinal outcome data, we will use longitudinal methods (e.g. mixed models) that are capable to deal with missing data.

Aim 2: Assess the implementation self-management process measures including: a) appropriate use of thermometer, b) application of pack to the "hot spot" for 5 consecutive days for 30 minutes (fidelity to self-management), c) utilization of supportive reinforcement, ***d) reactions/satisfaction of participants, and e) staff ratings and perceptions for replicability.***

Process and fidelity model: Our energetic interdisciplinary team has significant experience with rigorous process standards that will be enacted to educate participants in the protocol, provide reinforcement, and monitor fidelity, adherence and satisfaction with the treatment protocol in our highly supportive CTSA environment. We have created a feasibility/fidelity model [68,69] for our previous studies that also includes: recruitment, reach, retention, adherence, documentation, satisfaction, drop-out proportions, safety, and side effects. These will be collected by study personnel on the following logs:

a) Use of thermometer and b.) pack application: Participant treatment forms/checklist. These forms have been designed to assist participants to implement the intervention according to directions. The forms will undergo cognitive pre-testing and revision early in the award period prior to their use. These forms will help investigators answer the following questions: What was adherence to the protocol by the participants? What were the challenges and problems to adherence? The design includes check-boxes for missed applications and reasons to discourage lack of disclosure for lapses. We are cognizant of potential bias due to social desirability. During the instructional session research assistants will stress the need for participants to be honest, rather then feel they cannot report lapses in adherence.

c.) Reinforcement and d.) participant reactions: Retention telephone, email, and in-person reinforcement logs. Contact with participants is part of the monitoring protocol and critical to assuring adherence. Contact via supportive phone calls (§C.6.) or emails will also be used to determine whether there are difficulties with adherence, the presence of any side effects, safety, tolerability, comfort, concerns about the study, or problems with the disease process. Data pertinent to the operations of the trial, participant follow up, and the selection of the efficacy outcomes and measures will be evaluated during the treatment phases and at the conclusion of this study. Retention strategies include phone contact and contingency rewards. After completion of the intervention and control protocols, participants will be asked to complete a brief report form as part of the exit interviews by project director or research assistants. This survey will assess their views of the ease or difficulty with the treatment, as well as their satisfaction. Participants will be asked what did or did not meet their expectations and asked for suggestions on what could be done better if the study were redone.

Participants will be asked about visits to physicians or other providers during the study and asked to report if the study was discussed with them.

e.) Staff observation: Rating logs and scale. Dr. Kelechi and the project director will observe 10% of the participant education sessions on the treatment protocol to monitor fidelity to the participant visit protocols (screening, enrollment protocol, and DVD instruction conducted by research assistants).

Other: Participant identification, recruitment, reach and attrition logs. These logs will be kept using standardized forms completed by research assistants. These logs will be used to track the

proportion of persons enrolled in the study each week. To assure sufficient participants are recruited each month, Dr. Kelechi and the study coordinator will routinely check logs for completeness and follow-up, with additional orientation as needed if issues with participant identification and recruitment arise. We will also assess reach (e.g., how far away does participant live from study site, how did he/she learn about the study).

Data management logs. These logs will assess feasibility problems and document reasons for incomplete instrumentation and missing data.

Aim 2 analysis: To assess feasibility/fidelity study outcomes we will report the number of contacts with participants through telephone and email, the proportion who terminate the study early (drop-outs), proportion who are adherent to the study protocol, and proportion who report issues with tolerability and are satisfied with the treatment. Participants will complete a researcher developed exit end-of-study satisfaction survey at the final visit. Differences of fidelity outcomes will be compared between the two groups using chi-square tests or t-tests as appropriate (or equivalent non-parametric methods).

Data collection time points: There will be four study visits at which time study personnel will collect data on both participant groups. The PI and project manager will also collect data on research staff.

Baseline visit - demographic information (i.e., age, race, gender, co-morbid conditions, body mass index, number of previous ulcers, length of healing time, location, medications taken) and questionnaires on pain, physical activity and quality of life will be collected, affected leg or foot skin at the site of the newly healed ulcer to identify the "hot spot" will be imaged, procedural instructions for using the accelerometer given, protocol for self monitoring of temperature and self management of temperature elevation will be shown via DVD and written instructions given, and a test will be administered to assess understanding. Similar to our other studies, we will produce a YouTube video and take-home DVD of these instructions for standardization. Supplies include: thermometer, pack and freezer bag (given by Research Nexus staff after the research assistant has completed all study procedures) to be kept in freezer at all times except during treatment, a freezer thermometer to ensure temperatures are kept at O°F, skin marker, study logs and clipboard with attached pen for recording daily temperatures/maintenance and bolus cooling (times, dates)/freezer temperature, and timer (for 30 minutes of cooling). Baseline questionnaires to be administered include: VAS, BPI, IPAQ, SF-12, GDS, and the VEINES Qol or NPQ (as applicable).

Visit 1 – (month 1) - the daily month 1 temperature readings taken over 28 – 31 days (depending on the month) with the thermometer will be downloaded using a software program and averaged to establish the mean skin temperature. These data will be recorded in REDCap. The infrared thermometer will be programmed to sound an alarm when the readings are 2°F above the mean. Also at this visit the skin site will be imaged with the infrared camera and uploaded for comparison against the baseline reading. Data will also be uploaded from the accelerometer to assess physical activity. Any changes in demographics such as taking new medications will be evaluated, and the pain scales will be administered. Process measures will be collected including ease of use of thermometer, problems with study procedures, and fidelity to self-monitoring assessed (e.g., through downloaded temperature readings). Visit 1 questionnaires to be administered include: VAS, BPI, IPAQ, and the VEINES Qol or NPQ (as applicable).

Visit 2 – (month 3) – the daily months 2 and 3 temperature measurements and accelerometer

information will be downloaded, the skin site imaged, and demographic (i.e., changes in co-morbid conditions, new medications taken) and pain questionnaires administered. Process measures will be collected. Visit 2 questionnaires to be administered include: VAS, BPI, IPAQ, and the VEINES Qol or NPQ (as applicable).

Visit 3 – (month 6 final visit) – the daily months 4 – 6 temperature measurements and accelerometer information will be downloaded, the skin site imaged, demographic, pain and quality of life questionnaires administered. Process measures will be collected. Visit 3 questionnaires to be administered include: VAS, BPI, IPAQ, SF-12, GDS, and the VEINES Qol or NPQ (as applicable). During this final visit, an exit satisfaction survey ~~interview~~ will be conducted to ascertain information about overall feasibility, problems encountered, satisfaction, recommendations for changes to procedures, likelihood of maintaining/sustaining.

Ongoing supportive phone calls: Calls will be made to both groups 24 hours after the start of the study, weekly during weeks 1 – 4, and then monthly by research assistants. We will provide reinforcement of study procedures, solicit information about problems encountered, adherence, side effects, and leg temperatures and answer any questions (§Table 4).

Study staff: We will elicit feedback using a rating scale we have developed for our ongoing R01 that assesses the perceptions of staff, their beliefs regarding the sustainability of the intervention, likelihood of implementation into practice, and dissemination potential.

Relevant literature in support of or in disagreement with the potential results on pain:
We have elucidated the literature in support of monitoring and managing skin temperature, and our preliminary work with physical activity suggests a possible benefit (§Significance). The literature is replete with the beneficial effects of cooling injured tissue after acute trauma, orthopedic procedures, and dermatological therapies, however, less is known about the analgesic effects of cooling the skin on chronic ulcer pain [58,70-72], and in particular, about pain reduction of newly healed skin after prolonged healing. We are collecting data in our ongoing R01 to determine if cooling reduces pain, but are unable to analyze the data until the study is completed. If cooling provides pain relief, it may also positively influence physical activity and quality of life. Unfortunately, there is limited research to suggest reduced pain/discomfort from cooling previously ulcerated skin positively influences physical activity and quality of life in chronic populations. This study seeks to establish this role.

Timeline: Table 4 illustrated the time line for study activities.

TABLE 4: TIMELINE FOR PROPOSED RESEARCH PLAN

Activities	YEAR 1		2		3		4	
Training and hiring of staff, enrollment preparation, DVD design, SOP finalization, orientation of staff at Research Nexus, recruitment and marketing plans and implementation, participant enrollment, fidelity monitoring	■	■						
Rolling recruitment and enrollment, ongoing marketing, fidelity monitoring, reports		■	■					
Data collection including follow-up, reports		■	■	■	■	■	■	
Manuscript preparation/submission, reports						■	■	■

Impact and overall potential problems: In response to RFA-NR-15-001 Chronic Wounds: Advancing the Science from Prevention to Healing (R01), this study will elucidate the impact of cooling newly healed chronic venous leg and diabetic foot ulcers. Results of several studies, published in a meta-analysis [73], provide evidence that increased skin temperature predicts foot ulcers in patients with diabetes. Our research findings suggest increases in lower leg skin predicts VLUs [3]. We have studied self-monitoring skin temperature using hand-held infrared thermometers. These patient-centered approaches have received considerable attention over the past 20 years for the prevention of diabetic foot ulcers [2,61] and for the monitoring of venous leg ulcer-affected skin [3,42,43,50]. This study will further progress skin temperature's role in the self-management to prevent ulcer recurrence. We recognize that there are unmodifiable risk factors for ulcer recurrence such as diabetes, cardiac disease and older age [74], however, we emphasize that this study addresses a modifiable risk factor, persistent inflammation in the remodeling phase of healing. An efficacious cooling intervention that could reduce ulcer recurrence by 50% will reduce unnecessary health care utilization by thousands of afflicted individuals at potential cost savings of $10 billion. **Safety:** There have been no reported adverse events associated with our cooling treatment. We do recognize that some patients experience neuropathic-type pain (i.e., burning, tingling) and will be cognizant of the potential for the cooling therapy to exacerbate these symptoms. **Usability:** The thermometer selected for this study has a memory and thus, we predict that keeping track of skin temperature will be less cumbersome for participants. We will also assess acceptability of the accelerometer for physical activity monitoring. We will ask participants to record temperatures on logs in the event of a malfunction. Our experience with clinical trials, and in particular, being able to refine our study procedures for this trial, has allowed us to scrutinize our protocols to reduce the potential for unanticipated problems. **Retention:** We will compensate participants $250, will offer a successful contingency management plan that includes drawings for additional compensation, and will conduct frequent supportive phone calls. Our long-term goal is to offer an innovative and feasible clinical practice approach for the management of newly healed chronic VLUs and DFUs that are at high risk of ulcer recurrence. Prevention of these complications in a highly challenged population could result in less recurrence, fewer days lost from work, less use of pain medications, and improvements in physical activity and quality of life.

E. PROTECTION OF HUMAN SUBJECTS

Participants, 18 years-of-age and older, will be included in the study. The participants must be able to communicate in English. The study will include both genders and to ensure diversity, participants from various racial backgrounds representative of the area (~30% black/African-American, ~70% white, ~1% Hispanic/ /other) will be invited to participate. There are minimal risks for injury related to **MUSTCOOL**. There have been no reports of skin injury associated with the cryotherapy (cooling) intervention used in our ongoing R01, which is the same intervention that will be used in this proposed study to reduce inflammation (skin temperature). We have taken more precautions regarding avoidance of frostbite or other cooling related injuries (e.g. skin irritation) by reducing the area of the skin to be cooled, from regional (cuff applied to entire lower leg) to only a small, localized area of the foot or lower leg. Participants will be instructed to report symptoms such as tingling, prickling, and other sensations if noted during cooling. The informed consent and Health Insurance Portability and Accountability forms assure confidentiality of all information obtained during the study. Participants have the right to withdraw from the study at any time without any effect on the care they will receive in the future. Informed consent, approved by the Institutional Review Committee, will be obtained by study personnel and signed by the participant indicating willingness to participate in the study.

E.1. RISKS TO THE SUBJECTS

Human participants will be invited to participate in this study to test the preventive cooling intervention applied to newly healed skin of healed venous leg and diabetic foot ulcers. The goal is to prevent leg or foot ulcer recurrence. We will invite potentially eligible individuals to participate after screening them for adequate blood flow using an ankle brachial index (ABI). The healed area will be imaged with an infrared camera to capture a skin temperature "map" of the affected skin. Participants will then self-monitor the skin temperature of the highest area or "hot spot" with an infrared thermometer daily at home and apply a cooling or placebo pack (self-management) to the affected area for 30 minutes, three times each week. If an elevation is noted above baseline, they will apply the pack using a bolus-dosing regimen for 5 consecutive days. The study will be conducted over 6 months and require 4 visits including baseline, then months 1, 3 and 6. At each study visit, participants will complete the Geriatric Depression Scale (GDS) instrument. Participants with Total GDS scores greater than "5" (suggestive of depression) will be provided with 3 referrals to local area mental health care providers by study staff. Study staff will document the referral process in the participant's REDCap study eCRF. Process and safety monitoring data will be ascertained during weekly phone calls during the first month, then monthly. We will also inquire about safety and tolerability during phone calls and during study visits to include adherence (fidelity), side effects, comfort, and any other problems noted during the study. Both groups (cooling pack and placebo), during the baseline visit after eligibility is determined, will watch a DVD for the sole purpose of standardizing the instructions they receive. Participants will then be quizzed on their knowledge of the study procedures, and will demonstrate self-monitoring with the thermometer, self-managing skin temperature elevation with the pack, when to report problems, and the frequency of return visits.

Targeted/Planned Enrollment Table

Total Planned Enrollment: 180

TARGETED/PLANNED ENROLLMENT: **Number of Subjects**			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	1	1	2
Not Hispanic or Latino	107	71	178
Ethnic Category: Total of All Subjects*	180		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	31	21	52
White	77	51	23
Racial Categories: Total of All Subjects*	108	72	180

E.1.a. Human Subject Characteristics. Eligible men and women, 18 years of age and above will be approached, invited to participate, and screened to recruit a sample size of 180; 90 participants with venous leg ulcers will be randomized to receive the cooling pack or placebo and 90 participants with diabetic foot ulcers will be randomized to receive the cooling pack or placebo. The health status description of the population is based on the PIs previous experience with study participants from

previous studies and the demographics of South Carolina. It is anticipated that 95% will have at least one co-morbid chronic condition such as hypertension, diabetes, hypercholesterolemia, or arthritis, and approximately 60% will be obese. It is anticipated that the average age of the population will be 68 years old, 60% female, 40% male. We anticipate< 1% of the population will be Hispanic, 30% black/African American, ~70% white, which reflects the ethnic make-up of the recruitment area. We will include English speaking individuals only due to limited resources and the special needs of bilingual and culturally relevant protocol/materials. We will include individuals with co-morbid conditions such as diabetes, hypertension, and high cholesterol. Those with vascular conditions such as peripheral arterial disease will be excluded.

INCLUSION OF WOMEN AND MINORITIES

Women and underrepresented minorities will be included in the study within the available population. Although in this study race/ethnicity is not believed to have a direct impact on any of the research aims, special efforts will be made to recruit eligible underrepresented minority participants. The sites from which we will recruit participants have been selected because the underrepresented minority patient populations are 50% or higher. In the investigator's preliminary studies, minority participation ranged from 30–80%, and equal numbers of men and women, both black and white were easily recruited for inclusion. Due to the seasonal work issues related to the Hispanic population, it is anticipated that ~1% of the patient pool will be recruited for this study. The latest U.S. Census Bureau figures show that 15.1% of rural Americans are living in poverty. The national average is 13.2%. The poverty rate in South Carolina is 17.0%.

INCLUSION OF CHILDREN

Although vascular disorders appear as early as the first decade of life, venous leg and diabetic ulcers rarely occur in children, and therefore, children under 18 will not be recruited.

E.1.b. Sources of Materials. Materials obtained from the human participants include demographic data, circulation status (ABI), skin temperature mapping, physical activity with an accelerometer, and questionnaires that will be recorded in an electronic documentation web-based data management system (REDCap), from laptop/tablet computers. In the event of a failure to access REDCap, paper source documents have been created. All paper data will then be entered into the system as soon as possible. These documents will then be stored in the PIs office in a locked file. Demographic data about gender, age, ethnicity and pertinent medical history will be collected from the participants by self-report in order to describe the sample. These data will be used for research purposes only. REDCap is password protected and will only be accessible to select members of the research team, including the PI, project director and biostatistician.

E.1c. Potential Risks. After informed consent is obtained, screening data collected, and eligibility established, 180 individuals will be enrolled. Collecting data poses a minimal risk to confidentiality. All enrolled participants will be given instructions about the study procedures both verbally and in writing. The PI, project director, and biostatistician will have access to the data for analysis. If paper documents are necessary in the event of REDCap network failure, documents such as source documents, consent and HIPAA forms, questionnaires, and interview data will be stored in a locked file in the PIs office. The PI and project director will be the only study personnel with access to the paper files. There is minimal risk to the participants, as the cooling intervention has had no side effects noted in our ongoing study. All procedures are non-invasive and non- pharmacological. There may be some minor inconveniences to participants as the tests will take about 1 hour and they will have to remain in the supine position for approximately 20 minutes during the study to ascertain the ABI. Every effort will be made to make the

participants comfortable and provide privacy.

There are no known alternative treatments for this proposed intervention.

E.2. ADEQUACY OF PROTECTION AGAINST RISKS

E.2.a. Recruitment and Informed Consent The recruitment plan includes referrals from our well-established clinical sites that have been actively involved in our previous research studies. We have access to a diverse participant pool from rural settings from which to recruit. We will recruit underserved and underrepresented minorities. We have developed an extensive recruitment plan for our previous studies and have refined several strategies to ensure our enrollment targets are met for this study. Based on our recruitment metrics from our ongoing R01 and Dr. Kelechi's experience as the director of recruitment of MUSCs CTSA, we expect to enroll 1 subject for every 5 approached and screened (#1 reason for not enrolling is an abnormal ankle brachial index). The goal is to enroll ~6 subjects per month for 3 1/2 years, accounting for an expected attrition rate of ~25% (nature of the chronically-ill population with frequent hospital admissions). Our recruitment plan includes referrals from centers and practices (50% of participant will be referred), however we anticipate using other recruitment methods that we have found particularly successful including television, radio and billboard advertisements, use of our CTSA's SCResearch.org website, and our community based participatory research advisory groups. We have budgeted for these strategies accordingly. There is a need to incentivize center and practice referrals and to that end, we will provide $20 for every enrolled participant in the form of a "credit" gift card that can be used for whatever purposes deemed appropriate by the practice. **Retention:** We also have implemented a very successful contingency management approach for retention at one of our study sites (a drawing from a bowl at each visit with the opportunity to win from $1 to $100). The attrition rate for this site is ~17% compared to 30% (average of other sites' attrition rates).

We will provide packets of information about the study to referral sources that will provide information about calling a designated number to learn more about the study. Our study team will contact potentially eligible participants, discuss study details, and if interest is expressed in participating in the study, and the baseline study visit appointment will be arranged. The study will be conducted at the Research Nexus (CTSA) at MUSC, the Spartanburg Wound and Healing Center, and at East Carolina University. We will visit the referral sites on a regular basis to evaluate participant identification strategies and to assess the potential for selection bias. IRB approved flyers and marketing materials will be available at these sites, and disseminated through a network of local area provider clinics, and at the Charleston Veteran's Affairs Medical Center (VAMC-534). Participants will receive $250 compensation for participation: $25 first visit screening; $50 baseline visit; $50 for visits 2 and 3, $75 for visit 4.

The informed consent and Health Insurance Portability and Accountability Act (HIPAA) forms assure confidentiality of all information obtained during the study. Participants have the right to withdraw from the study at any time without any effect on the care they will receive in the future. Informed consent, approved by the Institutional Review Committee (IRB), will be obtained by the research nurses and signed by the patient indicating willingness to participate in the study. All study personnel have successfully completed the CITI Course in The Protection of Human Research Participants and Clinical Research Training through the National Institutes of Health. Certificates are on file at the IRB. A document, required by the IRB, will have recorded information regarding the time and date of consent, participant screening time and date, participant enrollment time and date, and study completion time and date. The research assistant obtaining this information will sign after each entry. To determine participant understanding of the nature of the study, the research assistant will assess understanding by asking the following questions (participants must be able to answer "yes" to all):

- briefly describe the purpose of the study.
- report the purpose of taking skin temperature and using the pack.
- describe the expectations for the study.
- demonstrate how to operate the thermometer and accelerometer.
- demonstrate how to apply pack.
- state that the study lasts for six months.
- report that they will attend a three additional study visits during the six-month intervention trial.
- state that they agree to wear compression stockings and/or diabetic footwear

E.2.b. Protection Against Risk

In the event of an unexpected medical or other event, the patient will be instructed to contact the research assistant. Based on the experience of the PI, it is anticipated that the risk of adverse events (AEs) will be acceptably very low. In the event of an AE, it will be recorded, the PI notified, and submitted to the IRB according to institutional procedures. All AEs will be reviewed by the PI and project director. Maximum efforts will be undertaken to ensure the safety of all participants. Study personnel will receive extensive training and orientation on procedures and protocols. Participants will be instructed on how to access the PI or research assistants in the event of a study-related question. In the event of study-related illness or injury, participants will be instructed on how to access health care. Although we do not anticipate any problems, we will address any that might arise such as reports of uncomfortable sensations in the leg or foot during or after pack application or the development of new leg or foot ulcers. This information will be recorded and if deemed as an AE by the research team, institutional procedures will be followed for reporting them. An order from the primary health provider is not required for participation in this study as there is oversight by the study MD, Dr. King and Dr. Flume at the Research Nexus. The accelerometer used to measure activity is small and does not pose any problems with being anchored to clothing.

Safety and side effects. There has been considerable attention given to the selection the cooling pack used in this study. We have refined the protocol, as noted in the overview to cool less surface area, targeting the "hot spot" only. We have taken precautions to use a cooling approach that does not aggressively or quickly reduce skin temperature, rather, the material used in the gel wrap does not freeze into a solid state, thus does not rapidly pull heat from the tissue. It is also enclosed in two polyethylene covers to prevent sticking to the skin. The pack will be anchored with a stretchy net "tubing" that can be pulled onto the foot or lower leg. In the event that the participant falls asleep or forgets to remove the pack during the procedure, the pack does not continue to transfer heat from the skin after approximately 15 minutes. There are minimal risks for injury to the skin using the methods of measuring skin temperature with the thermometer.

E.3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Conditioning the lower legs may improve some of the symptoms associated with leg ulcers such as pain and discomfort. The use of the accelerometer and Smartphone for providing patient feedback and giving reminders, involves patients in their own care and may help them feel empowered to reduce the negative effects of having a chronic disease. The long-term effects of having better conditioned lower legs may provide protection for ulcer relapse in high risk groups of patients, and could lead to greater health improvements if the potential to engage in more aerobic forms of physical activity is reached. This study involves minimal risk as a non- invasive study. The benefits outweigh the slight inconvenience to the patient in terms of anticipated new knowledge gained from the study.

E.4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study will provide valuable information to test an intervention that could potentially improve outcomes in participants vulnerable to lower leg and foot ulcer recurrence. The science of using infrared technology has led to advancements in ulcer prevention measures for both venous and foot ulcer participants. Non-pharmacotherapeutics (i.e., sequential compression devices, temperature mapping) have contributed to significant improvements in self-management of venous disease and diabetic foot complications. However, there has been little attention directed toward ulcer prevention strategies for chronic ulcer recurrence that incorporate an intervention that includes patient self-managing of signals of tissue damage such as inflammation. We propose to "re-invent" an old, yet effective cooling method that has negated the effects of inflammation associated with acute tissue injuries. This simple, inexpensive method, using a small pack, could improve current guideline-guided usual care by focusing on skin temperature, using maintenance cooling, and then bolus doses for elevations noted outside of the baseline "normal" temperature. This approach is novel in that it targets newly healed chronic ulcers. Finally, if the intervention is valid and reliable in this high-risk ulcer population, we envision our strategy will become a mainstream practice standard for the prevention of ulcer recurrence in the future.

E.5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

The study has a well-developed DSMP that has undergone NIH/NINR SRG review and approval. This plan is contained below:

Application number: 1 R01 NR015647-01

Project title: Monitoring and managing newly healed chronic leg and foot ulcer skin temperature: a cooling intervention (MUSTCOOL) to prevent ulcer recurrence

Principal investigator: Teresa J. Kelechi, PhD, RN

DATA SAFETY AND MONITORING PLAN (DSMP)

SECTION A. Monitoring Entity

Considering the study rationale, population, procedures, and the risk:benefit profile, the overall risk level for participation in this study is classified as: **Minimum Risk.** The study will employ the use of a Data Safety Monitoring Committee (DSMC) that will meet semi-annually across all years of the study. The DSMC members are charged with reviewing safety and trial progress and providing recommendations to the PI and MUSC IRB with respect to study continuation modification, and termination.

1) Data Safety Monitoring Committee (DSMC)

The study's DSMC is comprised of the following individual members:

- Dana King, MD, Study Physician (SP) and Chair - primary responsibility
- Naohiro Shibuya, DPM, Wound Expert (WE)
- Martina Mueller, PhD, Biostatistician (BS)
- Mohan Madisetti, MS, Project Manager (PM)

2) Individual Roles and Responsibilities

Principal Investigator, (PI). As PI, Dr. Kelechi will overall be responsible for the immediate protection of all human participant study participants.

Study Physician, **Dr. King** who is Chair of the Division of Family Medicine, Robert C. Byrd Health Science Center, Morgantown WV, has a master's degree in clinical research, and will serve as the Study Physician (SP) and Chair of the DSMC. Dr. King will correspond semi-annually with the DSMC to review de-identified cumulative AE study data to assess any impact on the safety of participants or on the ethics of the study. As the Chair and SP, Dr. King will be primarily responsible for the reviewing of all cumulative reported SAE that are related to study treatment, the provision of DSMC recommendations from data safety monitoring reports to the PI, MUSC's IRB and the NIH/NINR. Dr. King will be immediately notified of the occurrence of any

reportable SAE by the PM and will be provided with the necessary information to provide an informed recommendation in real-time regarding the protocol and human subject safety. Dr. King has no real or apparent conflict of interest that would affect his performance in this role on the study.

Wound Expert, **Dr. Shibuya** who is an Associate Professor of Surgery in the Division of Podiatry at Texas A&M Health Science Center, and specializes in wound management will serve as a member of the DSMC. As a member, Dr. Shibuya will also correspond semi-annually with the other members of the DSMC to review de-identified cumulative AE study data to assess any impact on the safety of participants or on the ethics of the study and provide expert safety recommendations. Dr. Shibuya has no real or apparent conflict of interest that would affect his performance in this role on the study.

Biostatistician, (BS). **Dr. Mueller** will be responsible for conducting semi-annual interim data analyses, generating semi-annual AE safety reports from the electronic study research database and disseminating de-identified information to all members of the DSMC. The interim data analyses will only include safety related results; analyses in regards to study outcome will not be performed. The interim AE safety reports will provide typology, frequency data and outcomes of all reported and documented AEs in the electronic study database. As a member of the DSMC, Dr. Mueller will also participate in semi-annual DSMC meetings.

Project Manager, (PM). **Mr. Madisetti** will be responsible for the classification of all reported adverse events (AE) and ensuring that all serious adverse events (SAE) are forwarded to the PI and SP in real time and in compliance with MUSC IRB and NINR's reporting requirements. In addition, and in conjunction with the PI, the Mr. Madisetti will be responsible for amending the protocol in accordance with the DSMC recommendations, submitting reportable SAEs to the IRB, and submitting annual Progress Reports to the NIH/NINR through MUSC's OSRP. As part of the DSMC, he will be responsible for: conducting monthly internal quality control audits on all participant records and notifying the PI of any deficiencies; assisting in the generation of ad hoc participant data safety reports as requested; and, the forwarding of reportable SAE to the NIH/NINR Program Official through MUSC's OSRP within 72hrs of IRB review and acknowledgement. Mr. Madisetti will also be responsible for following up on reported AEs to monitor outcomes and provide for the continuity of care for study participants.

SECTION B. Procedures for Safety, Risk and Confidentiality

1) Monitoring Study Safety

From the initial screening of participant by inclusion and exclusion criteria to the informed consent process to the provision of participant study instruction to staff training in Good Clinical Practices (GCP) and regulations pertaining to the Conduct of Human Participant Research to weekly contact with participants to internal quality control audits and protocol fidelity monitoring to the real-time review of AE by the SP and DSMC to the oversight of MUSC's IRB, procedures for monitoring study safety are consistently afforded throughout study. Specific procedures include:

- All participants will be screened for inclusion and exclusion per the protocol
- All participants will be fully informed as to all known risks and the possibility of risk from study participation in the informed consent process. These risks are minimal.
- AEs and changes in medical status will be elicited at every participant visit and contact.
- All participants will be given a 24 hrs. AE reporting phone number to the study nurse and instructed to notify the researchers of any/all suspected or experienced adverse events whether they believe them to be related to the intervention or not.

- The SP will have access to real-time AE study data and will be able to provide immediate recommendations to the PI and PM.
- The PM will track all reported participant AEs through to resolution. Please see Section C. 1 – 4.
- The BS shall generate semi-annual AE reports for the PI and DSMC to review.
- The PM will conduct a quarterly internal quality control audit of the study and all participant records to ensure compliance with MUSC IRB regulations and notify the PI of any deficiencies; the PM will work with the PM to correct any errors.
- The PI and/or designee will observe and evaluate ten (10%) percent of eligibility screening visits, informed consents and study instructions performed by IRB approved study personnel and provide feedback and/or retraining of study personnel if fidelity to both applicable federal regulations and the protocol is not observed.
- All investigators and researchers will maintain active CITI training.
- Investigator performance and compliance will be provided for through MUSC IRB and ORI study oversight.
- All reportable events, including protocol deviations will be forwarded to the NIH/NINR Program Official through MUSC's OSRP within 72hrs of IRB review and acknowledgement.

2) Minimizing Research-Associated Risk

Diligent study safety monitoring will be conducted by the PI and all members of the DSMC throughout the conduct of this study in compliance with the following required elements of MUSC IRB's continuing review process:

1. Tracking and follow-up of participant accrual including withdrawn consents will minimize risk by identifying, disclosing, and mitigating any potentially unknown risk(s) of harm to study participants. These risks are minimal.
2. Timely and appropriate reporting of informed consent process deficiencies, protocol deviations, privacy breaches, conflicts of interest, and/or changes in personnel.
3. Ongoing soliciting, monitoring and appropriate reporting of adverse event activities.
4. Timely and appropriate IRB submission of safety-related documents such as audit reports, sponsor progress reports, ISM reports, and other materials or communications that might impact the safe conduct of this study.
5. Active cooperation with the IRB, ACO, sponsor, and other applicable entities in the event of a random or for-cause internal or external audit.

Institution-Wide Assurances

This protocol will be conducted fully in keeping with the signed MUSC IRB Principal Investigator Statement of Assurance and Department Chair's Statement of Assurance, when submitted to the IRB as a required component of the MUSC IRB Human Research Review Application. An application will be submitted to the MUSC IRB if/when this project is approved and funded by NIH/NINR. Assurances include the following safety-related agreements, signed and dated by the PI.

3) Protecting Confidentiality of Participant Data

Participant Screening and Enrollment. All data from participants screened for the study will be entered into electronic study database. Designated research staff will collect, gather, and enter required data (written informed consent, HIPAA Authorization, medical history and demographics) onto study data forms. Screened patients who do not meet study eligibility will have specific screening data entered into the study database. The collected data will be helpful in examining the patient population and feasibility of enrollment criteria and will include gender, age, race and reason for exclusion. All dates will be shifted and other Personal Health Information (PHI) will be removed from the study database upon study completion. All data obtained from this

study will be used for research purposes only and will comply with Federal HIPAA regulations. Master Screening and Enrollment Logs will be maintained by the PM and will be used to prepare reports on accrual and attrition for the PI and DSMC.

Case Report Forms. All proposed study specific case report forms (source documents) for data collection will be designed by the PM in concert with the PI and BS, and transferred by the PM into electronic Case Report Forms (eCRFs) for use in the study's REDCap database. These study specific eCRFs source documents (study logs for correspondence, contact with provider, compensation and other forms such as pre-eligibility screens) will be coded by the participant's unique study ID# for all data collected including study instruments will be maintained in the participant research record and/or their electronic medical record that will be made accessible to study monitors. Completed instruments that require signature on a paper CRF will be scanned and uploaded into the study database to all for remote electronic safety monitoring as well as maintained on file in accordance with MUSC policies and applicable Federal Regulations for the Conduct of Human Participant Research.

Binders. The PM will prepare and maintain a participant-specific binder for each participant containing all non-eCRFs records. A regulatory file will also be maintained to include the IRB-approved Protocol, original Informed Consent documents, HIPAA forms and other study-related regulatory documents. All paper research records and CRFs will be maintained in a locked file cabinet, stored in a room for research files that is accessible only via a password protected entry system that features security cameras, within the College of Nursing. Access to the research records, study database and PHI's will be restricted to study personnel as approved by the PI and MUSC IRB. As with all studies conducted at MUSC, this study is also eligible for a random audit by MUSC Office of Compliance.

Data Processing. This study will use Research Electronic Data Capture (REDCap) for data capture and management. REDCap is a software toolset and workflow methodology for the electronic collection and management of research and clinical trials data. REDCap provides secure, web-based, flexible applications, including real-time validation rules with automated data type and range checks at the time of data entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The study-specific REDCap electronic database will be designed and developed by the PM in concert with the BS. The provision of REDCap is made available through the South Carolina Clinical & Translational Research (SCTR) Institute at MUSC with NIH Grant awards UL1RR029882 and UL1TR000062.

Data Security. Ensuring data security, compliance with 45 CFR 46 and maintaining the integrity of PHI is a top priority. MUSC has Standard Operating Procedures (SOP) to ensure a high level of data security while coordinating electronic and paper data management activities for clinical research trials. The REDCap study database will be hosted in the Biomedical Informatics secure data center at MUSC, a secure environment for data systems and servers on campus, and includes firewall, redundancy, failover capability, backups and extensive security checks. The secure data center has strict access control; only authorized core personnel may access the facility un-escorted. Only authorized users are allowed to connect to the network, and the security of the network is actively monitored. Power and environmental controls have several layers of backups, from interruptible power supplies to alternate and redundant feeds to the local utility company. The REDCap system administrator contributes to the maintenance of institutional disaster recovery and business continuity plans. Load balancers and a highly fault tolerant SAN infrastructure contribute to high availability.

The REDCap system itself has several additional layers of protection including password protection. Access to the data and its security is managed institutionally by sponsored login IDs through a Shibboleth login with an MUSC issued NetID and features a user account management filter that controls who can access the data and to what degree. All personnel must pass an employment background check before being issued an ID. Password complexity, history and expiration standards are implemented at the institutional level. Access to individual REDCap projects and their data is managed by the owner of the project. All transactions are securely delivered to the application using Secure Sockets Layer (SSL – SHA-1 with RSA Encryption; 2048-

bits). It is then transmitted internally (behind the firewall) to the database server. All transactions are logged at the server layer (httpd logging), application layers (REDCap logs activity to a database table), and the database layer, using both query and binary logging. This feature provides audit trails for all changes, queries, data exports and reports. MUSC Information security policies are available at: https://mainweb-v.musc.edu/security/policy/

Data Entry. Only MUSC IRB approved study personnel that are authorized to have access to the REDCap study database will be granted password access. Study personnel using computers that are connected to the Internet will directly enter data into the remotely housed database. As such, no electronic study data will be stored on hardrives and/or any portable electronic devices. Additionally, all personnel with access to the database will have current University of Miami CITI training in the Conduct of Human Subject Protections, and their respective institution's HIPAA and Information Security trainings that are completed annually. Each participant will be assigned a unique study identifier, all PHIs will be masked, and data exports will be limited to the PI, the PM and the BS for generating reports and the conduct of statistical data analysis.

Data Monitoring. Ongoing quality control procedures will be implemented for data collection, storage and processing. The PM will conduct monthly monitoring of the study database and generate a report for the PI to review at team meetings. Standing agenda items for these meetings will include participant recruitment and retention, AE's, protocol deviations, data integrity and overall study conduct. The PM will work to resolve and validate discrepant data. Discrepancies that warrant clarification will be sent to appropriate parties for review and resolution. All data entry and changes made in the study database by authorized study personnel will be automatically logged by REDCap, and provide a transparent visible audit trail for reviewers.

SECTION C.

Procedures for Identifying, Reviewing and Reporting Adverse Events

1) Identifying. Potential minimum risks identified for participants are outlined in the Protection of Human Participants and will also be outlined in the IRB-approved informed consent document. Additional unknown risks may occur and, if so, will be identified through diligent monitoring by the PM and the frontline research team throughout the conduct of this study. During the informed consent process, participants will be advised of the potential minimum risks of participation as identified in the IRB-approved informed consent document and reminded throughout the study that the researchers should be promptly informed about any concerns regarding potential side effects, adverse events, or clinical deterioration. Participants will also be instructed to notify the PI and/or designee of any suspected adverse events immediately if possible. Throughout the course of study enrollment, at each study visit, the researchers will elicit information about experienced AEs and monitor participant progress. The PM will maintain an electronic record of all reported adverse events and notify the PM and SP of all reportable events as they occur. The SP will have real-time access to the study database to review and monitor all SAEs that were reported as related to the intervention. The PM will generate and provide de-identified semi-annual administrative human participant safety reports for the DSMC to review participant progress, accrual and attrition rates. Additionally, the BS will generate semi-annual safety reports for the DSMC to provide for the monitoring of the frequency of all reported side effects and AEs.

2) Reviewing. Adverse events will be assessed and evaluated by the members of the DSMC according to the following MUSC's IRB Adverse Event Reporting Policy http://academicdepartments.musc.edu/research/ori/irb/HRPP/HRPP%20Guide%20Section%204.7:

- *Expected/Anticipated*—Identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.

- *Unexpected/Unanticipated*—Not identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.
- *More Prevalent*—Occurs more frequently than anticipated or at a higher prevalence than expected.
- *Serious*—Results in death, is life threatening, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability/incapacity, cancer, overdose, or causes a congenital anomaly/birth defect.

The relationship of adverse events to study participation will be determined by the DSMC according to the MUSC IRB Adverse Event Reporting Policy:

- *Unrelated*—There is not a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.
- *Possibly Related*—The adverse event may have been caused by the drug, device, or intervention, however there is insufficient information to determine the likelihood of this possibility.
- *Related*—There is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

3) Reporting. All reportable AE, SAE and unanticipated problems experienced by participants will be reported to the NIH/NINR and MUSC IRB in compliance with their Adverse Event Reporting Policy requirements, using the IRB's password protected on-line secure server adverse event reporting system. Within 24 hours after a reportable AE, SAE or unanticipated problem has been reported by the participant, it will be initially graded by the PM, forwarded to the study's SP for review and approval, and then will be submitted by the PI to MUSC IRB. The Institutional Official(s) will review the event and discuss the report with the IRB Chair and the Director of the Office of Research Integrity. After IRB review and acknowledgement, the PI will further review, and the PM will forward a copy of the reportable AE, SAE or unanticipated problem and IRB acknowledgement letter to the NIH/NINR Program Officer through MUSC's OSRP. The activities will be reported to the NIH/NINR within 72hrs. In addition, all cumulative reportable AE, SAE and unanticipated problems included in the ISM reports will be submitted to the NIH/NINR in the PI's Annual Progress Reports.

4) Examples of Potential Reportable Adverse Events: In accordance with MUSC IRB Adverse Event Reporting Policy, an AE is reportable is it meets all of the following criteria: 1) is unexpected 2) is related and/or possibly related, and 3) is serious and/or suggests that the research places participants or others at a greater risk of physical or psychological harm than was previously known or recognized. Additionally, per MUSC's policy all participant deaths, protocol deviations, complaints about the research, and breaches of confidentiality are reportable events. From our previous work among this comorbid population, an **example of an AE** would be the appearance of edema of the lower extremities that is related to the participant's underlying chronic venous insufficiency. Depending on the severity, the possible steps to be taken include referral to a medical provider, and/or withdrawing the participant from the study and inviting him or her to restart after acute symptoms subside. An **example of an SAE** would be the death of a participant from acute renal failure, which although would be viewed as unexpected and unrelated to the intervention is nonetheless a reportable serious event. No further steps would be taken except to review, grade and report the event to all applicable agencies. An **example of an unanticipated problem** would be the participant strains his or her back while taking their temperature of the ulcer "hot spot". The steps in this case would be to withdraw the participant from the study and invite him or her to restart the study after the strain has resolved. These events and problems will be reported in accordance with the IRB and NIH/NINR policy as noted in Section C.3.

SECTION D. Multi-site Monitoring and Compliance
This is not a multi-site study.

SECTION E. Assessment of External Factors
The PI will conduct a semi annual assessment of external factors through a review of literature related to new developments in the areas of diabetic foot ulcer and venous leg ulcer prevention, and other approaches that may have an impact on the safety of participants or on the ethics of the study. To determine whether any changes are necessitated to the study protocol, the DSMC will review any identified literature or product safety data that may pose as a potential impact to the risk benefit ratio study and/or safety of study participants.

SECTION F. Interim Analysis

Based upon our prior extensive research in this field among this same population and the minimal risk associated with the intervention, there is no stopping rule for this study. Accordingly, interim futility analysis will not be performed. However, the BS and PM will generate semi-annual qualitative interim analysis reports on a) adverse events; and b) data obtained during phone call and returned end-of-study surveys to understand issues related to the uptake, usability, and adoption of the cooling protocol among this population. We will evaluate the screening and enrollment procedures, barriers to participation and retention, including, safety, adherence, acceptability, technology problems (thermometer malfunction) encountered if any, and user feedback from the participants. The information gained from this structured process will inform the design for an implementation/dissemination study aimed to facilitate the use a leg and foot ulcer prediction/prevention standard of care.

F. REFERENCES/LITERATURE CITATIONS

1. Lavery LA, Higgins KR, Lanctot DR, Constantinides GP, Zamorano RG, Armstrong DG, Athanasiou KA, Agrawal CM. Home monitoring of foot skin temperatures to prevent ulceration. Diabetes care. 2004;27(11):2642-2647.
2. Bharara M, Schoess J, Armstrong DG. Coming events cast their shadows before: Detecting inflammation in the acute diabetic foot and the foot in remission. Diabetes/metabolism research and reviews. 2012;28 Suppl 1:15-20. doi: 10.1002/dmrr.2231.
3. Sayre EK, Kelechi TJ, Neal D. Sudden increase in skin temperature predicts venous ulcers: A case study. Journal of vascular nursing : official publication of the Society for Peripheral Vascular Nursing. 2007;25(3):46-50. doi: 10.1016/j.jvn.2007.06.002.
4. Enwemeka CS, Allen C, Avila P, Bina J, Konrade J, Munns S. Soft tissue thermodynamics before, during, and after cold pack therapy. Medicine and science in sports and exercise. 2002;34(1):45- 50.
5. Nemet D, Meckel Y, Bar-Sela S, Zaldivar F, Cooper DM, Eliakim A. Effect of local cold-pack application on systemic anabolic and inflammatory response to sprint-interval training: A prospective comparative trial. European journal of applied physiology. 2009;107(4):411-417. doi: 10.1007/s00421-009-1138-y. PubMed Central PMCID: PMC2762537.
6. Castellani JW, IK MB, Rhind SG. Cold exposure: Human immune responses and intracellular cytokine expression. Medicine and science in sports and exercise. 2002;34(12):2013-2020. doi: 10.1249/01.MSS.0000041400.21166.79.
7. Margolis DJ, Malay DS, Hoffstad OJ, Leonard CE, MaCurdy T, Lopez de Nava K, Tan Y, Molina T, Siegel KL. Prevalence of diabetes, diabetic foot ulcer, and lower extremity amputation among medicare beneficiaries, 2006 to 2008: Data points #1. *Data points publication series*. Rockville (MD)2011.
8. DeCotiis M, Konz EC. Minimizing complications of pain and dressing adherence in the treatment of venous leg ulcers. Ostomy/wound management. 2008;54(11):12-16.
9. Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: Incidence and prevalence in the elderly. Journal of the American Academy of Dermatology. 2002;46(3):381-386.
10. Gonzalez-Consuegra RV, Verdu J. Quality of life in people with venous leg ulcers: An integrative review. Journal of advanced nursing. 2011;67(5):926-944. doi: 10.1111/j.1365- 2648.2010.05568.x.
11. Heinen MM, Evers AW, Van Uden CJ, Van der Vleuten CJ, van de Kerkhof PC, Van Achterberg T. Sedentary patients with venous or mixed leg ulcers: Determinants of physical activity. Journal of advanced nursing. 2007;60(1):50-57. doi: 10.1111/j.1365-2648.2007.04376.x.
12. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, Gottrup F, Gurtner GC, Longaker MT. Human skin wounds: A major and snowballing threat to public health and the economy. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2009;17(6):763-771. doi: 10.1111/j.1524-475X.2009.00543.x. PubMed Central PMCID: PMC2810192.
13. Reeder S, de Roos KP, de Maeseneer M, Sommer A, Neumann HA. Ulcer recurrence after in- hospital treatment for recalcitrant venous leg ulceration. The British journal of dermatology. 2013;168(5):999-1002. doi: 10.1111/bjd.12164.
14. Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. The Cochrane database of systematic reviews. 2012;8:CD002303. doi: 10.1002/14651858.CD002303.pub2.
15. Lavery LA, Lavery DC, Hunt NA, La Fontaine J, Ndip A, Boulton AJ. Amputations and foot-related

hospitalisations disproportionately affect dialysis patients. International wound journal. 2013. doi: 10.1111/iwj.12146.

16. Hunt D. Diabetes: Foot ulcers and amputations. American family physician. 2009;80(8):789.
17. Bharara M, Schoess J, Nouvong A, Armstrong DG. Wound inflammatory index: A "proof of concept" study to assess wound healing trajectory. Journal of diabetes science and technology. 2010;4(4):773--779. PubMed Central PMCID: PMC2909505.
18. TJ, Mueller M, Zapka JG, King DE. The effect of a cryotherapy gel wrap on the microcirculation of skin affected by chronic venous disorders. Journal of advanced nursing. 2011;67(11):2337--2349. doi: 10.1111/j.1365--2648.2011.05680.x. PubMed Central PMCID: PMC3158956.
19. Kelechi TJ, King, D.E., Mueller, M., Pieper, B. A., Naohiro, S. Preventing venous leg ulcer with cryotherapy: A randomized clinical trial. Funded 2011 -- 2015 through National Institute of Nursing Research. Study ongoing. 2014.
20. Roaldsen KS, Biguet G, Elfving B. Physical activity in patients with venous leg ulcer----between engagement and avoidance. A patient perspective. Clin Rehabil. 2011;25(3):275--286. Epub 2010/12/15. doi: 0269215510371424 [pii] 10.1177/0269215510371424. PubMed Central PMCID: PMC3122380.
21. Roaldsen KS, Elfving B, Stanghelle JK, Talme T, Mattsson E. Fear--avoidance beliefs and pain as predictors for low physical activity in patients with leg ulcer. Physiotherapy research international : the journal for researchers and clinicians in physical therapy. 2009;14(3):167--180. doi: 10.1002/pri.433.
22. Kelechi TJ, Mueller M, Spencer C, Rinard B, Loftis G. The effect of a nurse--directed intervention to reduce pain and improve behavioral and physical outcomes in patients with critically colonized/infected chronic leg ulcers. Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN. 2014;41(2):111--121. doi: 10.1097/WON.0000000000000009.
23. Kelechi TJ, Green A, Dumas B, Brotherton SS. Online coaching for a lower limb physical activity program for individuals at home with a history of venous ulcers. Home Healthc Nurse. 2010;28(10):596--605. Epub 2010/11/09. doi: 10.1097/NHH.0b013e3181f7e99d 00004045--201011000--00004 [pii].
24. Bennett NT, Schultz GS. Growth factors and wound healing: Part ii. Role in normal and chronic wound healing. The American Journal of Surgery. 1993;166(1):74--81.
25. Demidova--Rice TN, Hamblin MR, Herman IM. Acute and impaired wound healing: Pathophysiology and current methods for drug delivery, part 1: Normal and chronic wounds: Biology, causes, and approaches to care. Advances in skin & wound care. 2012;25(7):304.
26. Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: Molecular and cellular mechanisms. Journal of Investigative Dermatology. 2007;127(3):514--525.
27. Loots MA, Lamme EN, Zeegelaar J, Mekkes JR, Bos JD, Middelkoop E. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous ulcers versus acute wounds. Journal of Investigative Dermatology. 1998;111(5):850--857.
28. Wetzler C, Kämpfer H, Stallmeyer B, Pfeilschifter J, Frank S. Large and sustained induction of chemokines during impaired wound healing in the genetically diabetic mouse: Prolonged persistence of neutrophils and macrophages during the late phase of repair. Journal of Investigative Dermatology. 2000;115(2):245--253.

29. McCarty SM, Percival SL. Proteases and delayed wound healing. Advances in wound care. 2013;2(8):438---447.
30. McKelvey K, Xue M, Whitmont K, Shen K, Cooper A, Jackson C. Potential anti---inflammatory treatments for chronic wounds. Wound Practice & Research: Journal of the Australian Wound Management Association. 2012;20(2):86.
31. Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF. Impaired wound healing. Clinics in dermatology. 2007;25(1):19---25.
32. Mi Q, Rivière B, Clermont G, Steed DL, Vodovotz Y. Agent-based model of inflammation and wound healing: Insights into diabetic foot ulcer pathology and the role of transforming growth factor-β1. Wound Repair and Regeneration. 2007;15(5):671---682.
33. Wang X---J, Han G, Owens P, Siddiqui Y, Li AG. Role of tgfβ---mediated inflammation in cutaneous wound healing. Paper presented at: Journal of Investigative Dermatology Symposium Proceedings2006.
34. Raffetto JD. Dermal pathology, cellular biology, and inflammation in chronic venous disease. Thrombosis research. 2009;123 Suppl 4:S66---71. doi: 10.1016/S0049---3848(09)70147---1.
35. Raffetto JD. Inflammation in chronic venous ulcers. Phlebology / Venous Forum of the Royal Society of Medicine. 2013;28 Suppl 1:61---67. doi: 10.1177/0268355513476844.
36. Raffetto JD, Mannello F. Pathophysiology of chronic venous disease. International angiology : a journal of the International Union of Angiology. 2014;33(3):212---221.
37. Demidova---Rice TN, Hamblin MR, Herman IM. Acute and impaired wound healing: Pathophysiology and current methods for drug delivery, part 1: Normal and chronic wounds: Biology, causes, and approaches to care. Advances in skin & wound care. 2012;25(7):304---314. doi: 10.1097/01.ASW.0000416006.55218.d0. PubMed Central PMCID: PMC3428147.
38. Kelechi TJ, Haight BK, Herman J, Michel Y, Brothers T, Edlund B. Skin temperature and chronic venous insufficiency. Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN. 2003;30(1):17---24. doi: 10.1067/mjw.2003.10.
39. Lavery LA, Armstrong DG. Temperature monitoring to assess, predict, and prevent diabetic foot complications. Current diabetes reports. 2007;7(6):416---419.
40. Lavery LA, Higgins KR, Lanctot DR, Constantinides GP, Zamorano RG, Athanasiou KA, Armstrong DG, Agrawal CM. Preventing diabetic foot ulcer recurrence in high---risk patients: Use of temperature monitoring as a self---assessment tool. Diabetes care. 2007;30(1):14---20. doi: 10.2337/dc06---1600.
41. Armstrong DG, Holtz---Neiderer K, Wendel C, Mohler MJ, Kimbriel HR, Lavery LA. Skin temperature monitoring reduces the risk for diabetic foot ulceration in high---risk patients. The American journal of medicine. 2007;120(12):1042---1046. doi: 10.1016/j.amjmed.2007.06.028.
42. Kelechi TJ, McNeil RB. A prospective, descriptive study of hour---to---hour and day---to---day temperature variability of skin affected by chronic venous disorders. Ostomy/wound management. 2008;54(4):18---34.
43. Kelechi TJ, Michel Y. A descriptive study of skin temperature, tissue perfusion, and tissue oxygen in patients with chronic venous disease. Biological research for nursing. 2007;9(1):70---80. doi: 10.1177/1099800407299424.
44. Barone S, Paoli A, Razionale AV. Assessment of chronic wounds by three---dimensional optical imaging

based on integrating geometrical, chromatic, and thermal data. Proceedings of the Institution of Mechanical Engineers. Part H, Journal of engineering in medicine. 2011;225(2):181-193.

45. Bagavathiappan S, Saravanan T, Philip J, Jayakumar T, Raj B, Karunanithi R, Panicker TM, Korath MP, Jagadeesan K. Infrared thermal imaging for detection of peripheral vascular disorders. Journal of medical physics / Association of Medical Physicists of India. 2009;34(1):43-47. doi: 10.4103/0971-6203.48720. PubMed Central PMCID: PMC2804148.
46. Lahiri BBB, S.; Jayakumar, T.; Philip, J. Medical applications of infrared thermography: A review. Infrared Physics & Technology. 2012;55(4):221-235.
47. Dargaville TR, Farrugia BL, Broadbent JA, Pace S, Upton Z, Voelcker NH. Sensors and imaging for wound healing: A review. Biosensors & bioelectronics. 2013;41:30-42. doi: 10.1016/j.bios.2012.09.029.
48. Mehmood N, Hariz A, Fitridge R, Voelcker NH. Applications of modern sensors and wireless technology in effective wound management. Journal of biomedical materials research. Part B, Applied biomaterials. 2014;102(4):885-895. doi: 10.1002/jbm.b.33063.
49. Mirabella C, Ballandi, S., Granziani, G., Tolomei, L., Manetti, L., Fortuna, D. Hemodynamic 3d infrared thermal stereoscopic imaging (tsi) investigation in chronic vascular leg ulcers: A feasibilty study. Wounds. 2011;23(9):276-284.
50. Kelechi TJ, Good A, Mueller M. Agreement and repeatability of an infrared thermometer. Journal of nursing measurement. 2011;19(1):55-64.
51. Bagavathiappan S, Philip J, Jayakumar T, Raj B, Rao PN, Varalakshmi M, Mohan V. Correlation between plantar foot temperature and diabetic neuropathy: A case study by using an infrared thermal imaging technique. Journal of diabetes science and technology. 2010;4(6):1386-1392. PubMed Central PMCID: PMC3005049.
52. Cunningham JE, Kelechi T, Sterba K, Barthelemy N, Falkowski P, Chin SH. Case report of a patient with chemotherapy-induced peripheral neuropathy treated with manual therapy (massage). Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2011;19(9):1473-1476. doi: 10.1007/s00520-011-1231-8.
53. Freiman A, Bouganim N. History of cryotherapy. Dermatology online journal. 2005;11(2):9.
54. Bodendorf MO, Grunewald S, Simon JC, Paasch U. Efficacy and cosmetic results of contact gel cooling of the skin during non-ablative laser procedures. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG. 2008;6(8):647-652. doi: 10.1111/j.1610-0387.2008.06610.x.
55. Armstrong DG, Sangalang MB, Jolley D, Maben F, Kimbriel HR, Nixon BP, Cohen IK. Cooling the foot to prevent diabetic foot wounds: A proof-of-concept trial. Journal of the American Podiatric Medical Association. 2005;95(2):103-107.
56. Khoshnevis S, Craik NK, Diller KR. Cold-induced vasoconstriction may persist long after cooling ends: An evaluation of multiple cryotherapy units. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2014. doi: 10.1007/s00167-014-2911-y.
57. Nicolaides AN, Allegra C, Bergan J, Bradbury A, Cairols M, Carpentier P, Comerota A, Delis C, Eklof B, Fassiadis N, Georgiou N, Geroulakos G, Hoffmann U, Jantet G, Jawien A, Kakkos S, Kalodiki E, Labropoulos N, Neglen P, Pappas P, Partsch H, Perrin M, Rabe E, Ramelet AA, Vayssaira M, Ioannidou E, Taft A. Management of chronic venous disorders of the lower limbs: Guidelines according to scientific evidence. International angiology : a journal of the International Union of

Angiology. 2008;27(1):1---59.
58. Muldoon J. Skin cooling, pain and chronic wound healing progression. British journal of community nursing. 2006;11(3):S21, S24---25.
59. Bharara M, Viswanathan V, Cobb JE. Cold immersion recovery responses in the diabetic foot with neuropathy. International wound journal. 2008;5(4):562---569. doi: 10.1111/j.1742--- 481X.2008.00454.x.
60. Shibuya N, Schinke TL, Canales MB, Yu GV. Effect of cryotherapy devices in the postoperative setting. Journal of the American Podiatric Medical Association. 2007;97(6):439---446.
61. Roback K. An overview of temperature monitoring devices for early detection of diabetic foot disorders. Expert review of medical devices. 2010;7(5):711---718. doi: 10.1586/erd.10.35.
62. Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini---cog: A cognitive 'vital signs' measure for dementia screening in multi---lingual elderly. International journal of geriatric psychiatry. 2000;15(11):1021---1027.
63. Averbuch M, Katzper M. Assessment of visual analog versus categorical scale for measurement of osteoarthritis pain. Journal of clinical pharmacology. 2004;44(4):368---372. doi: 10.1177/0091270004263995.
64. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the brief pain inventory for chronic nonmalignant pain. The journal of pain : official journal of the American Pain Society. 2004;5(2):133---137. doi: 10.1016/j.jpain.2003.12.005.
65. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire: 12---country reliability and validity. Medicine and science in sports and exercise. 2003;35(8):1381---1395. doi: 10.1249/01.MSS.0000078924.61453.FB.
66. Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluation of outcomes in chronic venous disorders of the leg: Development of a scientifically rigorous, patient---reported measure of symptoms and quality of life. Journal of vascular surgery. 2003;37(2):410---419. doi: 10.1067/mva.2003.152.
67. Lee JM, Kim Y, Welk GJ. Validity of consumer---based physical activity monitors. Medicine and science in sports and exercise. 2014. doi: 10.1249/MSS.0000000000000287.
68. Robbins LB, Pfeiffer KA, Wesolek SM, Lo YJ. Process evaluation for a school---based physical activity intervention for 6th--- and 7th---grade boys: Reach, dose, and fidelity. Evaluation and program planning. 2014;42:21---31. doi: 10.1016/j.evalprogplan.2013.09.002.
69. Spillane V, Byrne MC, Byrne M, Leathem CS, O'Malley M, Cupples ME. Monitoring treatment fidelity in a randomized controlled trial of a complex intervention. Journal of advanced nursing. 2007;60(3):343---352. doi: 10.1111/j.1365---2648.2007.04386.x.
70. Hampton S. A small study in healing rates and symptom control using a new sheet hydrogel dressing. Journal of wound care. 2004;13(7):297---300.
71. Hampton S. A focus on actiformcool in the reduction of pain in wounds. British journal of community nursing. 2007;12(9):S37---42.
72. Zoellner P, Kapp H, Smola H. Clinical performance of a hydrogel dressing in chronic wounds: A prospective observational study. Journal of wound care. 2007;16(3):133---136.
73. Houghton VJ, Bower VM, Chant DC. Is an increase in skin temperature predictive of neuropathic foot

ulceration in people with diabetes? A systematic review and meta-analysis. Journal of foot and ankle research. 2013;6(1):31. doi: 10.1186/1757-1146-6-31. PubMed Central PMCID: PMC3750703.

74. Finlayson K, Edwards H, Courtney M. Factors associated with recurrence of venous leg ulcers: A survey and retrospective chart review. International journal of nursing studies. 2009;46(8):1071-1078. doi: 10.1016/j.ijnurstu.2008.12.012.

G. CONSULTANTS

Letters of Support have been uploaded.

H. FACILITES AVAILABLE

The proposed clinical trial will be conducted at MUSC at the Research Nexus and builds on a referral network of existing professional collaborations both within and outside of the University.

MEDICAL UNIVERSITY OF SOUTH CAROLINA

College of Nursing. Office areas at MUSC are well lighted, well ventilated, and appropriately appointed for scholarly activities, paperwork, and modes of communication (voice, data, analog, digital, etc.) that are common and appropriate at a contemporary health professional university and academic medical center. Competent support staff and standard office services are readily available to facilitate the academic and scientific activities of faculty, trainees, and technical staff. Dr. Kelechi and her research team have adequate office space in the College of Nursing to implement this research study.

CON Office of Research. The College of Nursing has made a commitment to develop an intensive research environment and has a dedicated Office of Research (OR). The OR advances the research and scholarship mission of the CON and university with a focus on facilitating the efforts of faculty and graduate students to obtain external funding to support research. The OR coordinates faculty and graduate student access to a wide range of support services available within the CON and university. The OR is staffed with the Associate Dean of Research, grants specialist, program manager, scientific editor, pre-and post-award manager, methodologist, statisticians, and a data manager. The OR provides extensive pre- and post-award support for all funded projects, including assistance with biostatistics, grant and manuscript development, technical editing and manuscript assistance, grants management, and reporting and regulatory issues.

Office of the Chief Information Officer, Information Services (OCIO-IS). The FOOTFIT project will include data transferred from accelerometers and Smartphones, and some hard copy questionnaire data related to feasibility, as well as results of physical functioning tests (walking, range of motion, strength) performed at the study site in Spartanburg, SC. The computer and network infrastructure to gather, store and analyze these data securely is managed by the Office of the Chief Information Officer, Information Services (OCIO-IS). Information Services, a division of the Office of the Chief Information Officer (OCIO), manages MUSC's campus-wide data and voice communication network as well as other core infrastructure systems and applications.

South Carolina Clinical Translational Research Institute (SCTR). We have utilized the SCTR clinical and laboratory services for our other studies and for early phases of our iterative design based SMASH project. SCTR serves as the catalyst for changing the culture of biomedical research, facilitating sharing of resources and expertise, and streamlining research-related processes to bring about large-scale changes in the clinical and translational research efforts in South Carolina. SCTR facilitates the kind of cross-disciplinary research that can provide answers to complex problems by coordinating expertise and resources throughout the state. SCTR also catalyzes the development of teams of researchers with unique and complimentary perspectives who will create and implement effective, culturally sensitive primary and secondary prevention and treatment interventions based on fundamental discoveries. SCTR has robust collaborations with affiliate members including the University of South Carolina, Health

Sciences South Carolina, Clemson University, South Carolina State University, Claflin University, Greenwood Genetics Center, South Carolina Research Authority, and VA Medical Centers to expand innovative research and training activities across the SCTR region. Health Sciences South Carolina is a public/private partnership of the state's largest healthcare systems and three SC research universities (MUSC, USC and Clemson University).

The SUCCESS Center, one of the initiatives of the SCTR provides links across the campus and across the state for the researchers seeking expertise or services in a variety of research areas. The Recruitment Core, head by PI, Dr. Teresa Kelechi, provides investigators with strategic strategies to recruit and retains subjects for their particular study designs. REDCap Database and Survey Service is run by the SUCCESS Center. REDCap is being used on the proposed project. It was initiated at Vanderbilt University and includes more than 70 active institutional partners from CTSA, GCRC, RCMI funded institutions, including MUSC, and others. REDCap (Research Electronic Data Capture) is a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. REDCap Survey is a powerful tool for building and managing online surveys. Surveys can be created and designed in a web browser, collect responses from survey participants on line or from printed PDF of the survey.

The Biomedical Informatics Program is another important resource for our MUSTCOOL project. The program's goal is to integrate the informatics programs of SCTR and HSSC institutions, their medical centers, physician networks, major healthcare systems and populations across South Carolina while also providing robust tools for researchers. The MUSTCOOL project will utilize the data base storage and analysis available through this program.

The Department of Public Health Sciences (*formerly Division of Biostatistics and Epidemiology/DBE*), has more than 30 faculty members with expertise in biostatistics and epidemiology, many with joint appointments in other areas of MUSC. As an example, Co-I, Dr. Martina Mueller, is a faculty member in the Department and has an appointment in the College of Nursing as well. This enables frequent impromptu meetings among the group in addition to regular research meetings. DBE houses and supports two institutional research resource units: the Collaborative Unit and the Data Coordination Unit. The Department has two units and extensive computing resources. Faculty members in the Biostatistics Unit have expertise in such areas as categorical, longitudinal, multivariate, survival, recurrent events, multiple outcomes, and Bayesian biostatistical methods. They coordinate various clinical trials and health related studies on national and local level and in single and multisite programs, and they develop innovative models and methods for efficient and informative data analysis by incorporating scientific knowledge from the pertinent biological and clinical areas.

The South Carolina Research Nexus, available through SCTR is another valuable resource to the FOOTFIT project. Our team has utilized the Research Nexus as an evaluation site for several studies including our cryotherapy study and physical activity development pilot work. The Research Nexus is a specialized, JCAHO-accredited, patient care unit whose goal is to both facilitate patient-oriented research in a cost-effective manner and help strengthen the discipline of clinical and translational science. The Research Nexus supports clinical and translational research projects within the institution and SCTR affiliate members as well as pilot studies that may lead to future NIH or other sources of peer-reviewed

clinical/translational research grant support. Two other important functions of the Research Nexus include furnishing a clinical research training environment and assurance of research subject safety through the Research Nexus's Research Subject Advocate, whose role is to oversee the safe implementation of research studies within the unit. The specialized staff of the Research Nexus consist of research nurses, laboratory personnel, nutritionists, IT specialists, and professional/administrative personnel. A core laboratory, fully-equipped outpatient clinic, dental suite, and imaging suite comprise the highly-technical physical facilities that are on hand to support research. Research Nexus laboratory staff are qualified and trained in processing a myriad of sample types, including serum, plasma, urine, stool and breast milk. In addition, the staff is proficient in the latest DNA/RNA isolation techniques and offer a wide variety of specialized assays. We have utilized the Research Nexus core clinical services to perform physical and functional measurements in our other studies and for some of our physical activity development and pilot work.

RESEARCH RESOURCES

Research Development and Administration

The MUSC research infrastructure includes pre- and post-award functions reporting to the Vice President for Academic Affairs & Provost through the Associate Provost for Research. The Office of Research Development focuses on program and proposal development, identifies funding opportunities, develops proposal concepts, networks faculty members with complementary interests, provides grant-writing consultation and workshops, offers pre-submission critiques, compiles institutional data, and prepares competitive proposals for research resources and research training. The Office of Research and Sponsored Programs (ORSP) handles certifications and assurances, ensures that policies and procedures are followed, helps prepare budgets, negotiates terms and conditions, maintains proposal and awards data, administers the program of intramural research grants, and oversees re-budgeting and close-out activities. ORSP is the institutional interface with Grants.gov and coordinates all aspects of electronic research administration. The Office of Research Integrity provides oversight and staffing for activities focused on compliance with regulations for research involving humans, vertebrate animals, and biohazard agents. It also coordinates management of conflict of interest, financial disclosure, and scientific integrity issues.

Protection of Human Subjects

The participation of human subjects in research falls under the jurisdiction of federal regulations (45 CFR 46 and 21 CFR 50 and 56). MUSC investigators are granted the privilege of working with human subjects under normal assurance to the government that such research complies with regulations protecting human subjects. The university has a federal-wide assurance for research with human subjects (FWA 00001888, Feb. 2002), and is in compliance with federal policy governing use of human subjects. Individuals involved in human subject research at MUSC are required to complete the Collaborative IRB Training Initiative (CITI) offered on line by the University of Miami. Registration and course work can be found at http://www.miami.edu/citireg. All human subject protocols are reviewed through an academic Institutional Review Board (IRB) process. The Office of Research Integrity coordinates the activities of three IRB committees.

Compliance

The MUSC University Compliance Program is a proactive program to ensure full compliance with all applicable policies, procedures, laws, and regulations. This involves a confidential Compliance Helpline to encourage all members of the MUSC community to ask questions or voice concerns about laws and regulations on such topics as coding and billing, research integrity, professional ethics, human subjects,

animal research, biological safety, conflict of interests, and patient confidentiality. The program office proactively trains employees and facilitates discovery of concerns, followed by appropriate investigation into problem areas and timely resolution of issues. This program directly assists MUSC's management at all levels in maintaining and enhancing an environment where ethics are paramount considerations in strategic and operational decisions throughout the organization.

I. INVESTIGATOR BROCHURE

Not Applicable

J. APPENDIX