A Test of the Safety, Effectiveness, and Acceptability of an Improvised Dressing for Sickle Cell Leg Ulcers in a Tropical Climate

NCT04479618

As of June 3, 2021

IV. Project Proposal

1. Introduction:

a. Review of Literature

Sickle Cell Leg Ulcers:

One in 300 Jamaicans have the most serious form of sickle cell disease (HgbSS), and of these, between 30% and 70% will suffer from sickle cell leg ulcers (SCLUs).[1–4,10] Although leg ulcers can affect any age group, by far the majority of sufferers develop their first SCLUs when they are between the ages of 10 and 19.[2,18]

The SCLUs occur in a younger population, so comorbid conditions such as hypertension, diabetes, peripheral arterial or venous disease, and congestive heart failure are uncommon.[16]

SCLUs are found most often along the malleoli, followed by the shins.[8,10] SCLUs heal 16 times slower than notoriously difficult to heal venous leg ulcers, and in some patients, they never heal, even with decades of expert wound management.[3,5–7,16] SCLUs often enlarge during the first four weeks of management, and when they do close, they have a higher incidence of recurrence.[8,16]

SCLUs have an even more negative impact on patient physical quality of life when compared to a myocardial infarction, kidney dialysis, or diabetic foot ulcer.[17] Pain is unrelated to SCLU size and required high doses of opioid, which does not always provide adequate control.[3,9,11,15,18,19] Because SCLUs often compromise education and employment opportunities, improving wound care for this population benefits the entire community in which they live.[9–11]

Singh and Minniti, and Clare, Serjeant, et al., defined chronic SCLUs as those with greater than one month duration.[3,20] Factors affecting the formation and healing of SCLUs or progression to a chronic condition remains elusive.[21] The correlation with poverty, high serum lactate dehydrogenase, and lower leg venous system damage with SCLUs has been reported.[3,7,10,18,20] Higher base line hemoglobin levels offer a protection against SCLUs.[3] Slough, which is a byproduct of inflammation, is a hallmark of these chronic wounds.[4,22] Compression therapy and bedrest improve healing of SCLUs, just as they improve the healing of venous ulcers not associated with sickle cell disease.[3,15,18]

In 2014, Cochrane reviewers found only one study of interventions for SCLUs demonstrating significantly improved outcomes, and it was judged to be of very low quality.[8,23] An RGD peptide matrix gel was found superior to saline in 55 patients who had SCLUs of at least one month duration.[23] However, it is entirely possible that the benefit was due to the moist healing environment fostered by the gel itself, rather than the "active" ingredient within it.[24–27]

Experts in the field concur that because no other topical wound management method has been shown to be more effective, often painful wet-to-dry (saline soaked gauze) dressings remain the standard therapy for SCLUs, and papaya is frequently used to debride these ulcers, despite the risk of damage to healthy tissue.[7,8,15,17,19,28]

Unique challenges of wound management in tropical developing countries:

Unrelenting heat, poor sanitation, and insufficient knowledge contribute to a disabling overall wound prevalence of over 20% in many tropical developing countries.[30,31]

Wounds in these countries tend to be poorly managed at high cost.[31] Moist wound management is the accepted standard of care.[18,32–34] However, although wound experts in remote rural areas often choose dressing materials which are moist when applied, most of their choices (e.g., crushed leaves) are not able to sustain the moisture levels needed for optimum wound healing.[35,36]

Most of the relatively few research studies on wounds in tropical developing countries were conducted in the 1970s and 1980s.[27,30] However, in 2009, several non-profit organizations, including the Association for the Advancement of Wound Care (AAWC) Global Alliance, and Handicap International worked with the World Health Organization (WHO) to form the World Alliance for Wound and Lymphedema Care (WAWLC).[37] WAWLC promotes wound care research and education in developing countries, representing a renewed interest in this neglected field.[37] Recently, several wound journal editorials have highlighted this need, as well.[37–39]

Although health professionals are scarce in rural areas of developing countries, nurses often educate village health workers (VHWs) to promote health and provide basic interventions such as wound management.[40–42] Experts agree that achieving effective wound management in this setting will require educating the lay health providers - VHWs, traditional health providers, and family members - who provide health care in these areas.[43–45] Teaching wound care to VHWs was found to be effective, resulting in statistically significant improvements in the morbidity of the population they served.[45]

Rural patients can also be taught wound self-care. In a study of wounds from guinea worm in Ghana, only 0.5% of the sufferers had gone to clinics for their wounds.[46] Patients who were given antibiotics and instructions for cleaning, soaking, and dressing wounds by the researchers were disabled for an average of 2.4 weeks, as compared to disability for 5.3 weeks among controls.[46] However, because the study dressing materials are not readily available in impoverished rural areas, such efforts are not sustainable.

The proposed study is a direct outgrowth of a critical review of the literature (Benskin, 2013, attached) addressing the question, "What is the evidence base for topical wound treatments and dressings that are affordable and available in developing countries?"[27] The question arose out of a desire to improve wound care by providing evidence-based education in this challenging setting. Available, inexpensive, culturally acceptable materials are preferable for use as wound dressings.[35] However, evidence to support safe, effective wound management methods using supplies readily available in impoverished rural areas is absent.[27,35]

An exhaustive literature search, conducted with the assistance of a librarian specializing in complementary and alternative medicine, yielded evidence for only five potentially suitable dressing choices: honey, furniture foam, boiled potato peel, plastic food wrap (PW), and banana leaf (BL).[27] Periodic subsequent searches of the literature have provided further support for honey, PW, and BL, but identified no additional materials to explore.[47,48] A brief summary of the

pertinent aspects of the aforementioned published critical review of the literature[27] and the more recent studies is provided here.

Improvised dressings literature:

Honey is an ancient wound treatment.[49] Honey's high osmolality prevents bacterial growth, decreases maceration, and encourages healing.[50,51] Honey also has other properties which may independently inhibit bacterial growth.[50,51] However, all honey is not equally efficacious: The composition of honey is influenced by the species of bee and the plant origin of the nectar, as well as processing and storage procedures.[50,51] Therefore, study results may not be generalizable across sources.[50] Honey quality in the tropics is extremely variable. While thick honey is available in urban supermarkets, and some local honey in southern India has excellent bactericidal properties, in rural areas of West Africa and Southeast Asia some honey is so watery that mold readily grows on it.[52] Honey's osmolality increases wound exudate, which may quickly dilute it over tenfold.[52]

A series of eleven studies of honey on wounds conducted by Subrahmanyam, of Solapur, India, provided the main source of data for two major reviews, both of which concluded that although honey is supported by biological plausibility, the clinical evidence is weak.[48,50] Many of Subrahmanyam's studies had serious methodological flaws. For example, a 1998 prospective RCT of 50 partial-thickness burn patients divided into two equal groups compared honey dressings to silver sulfadiazine.[53] The researcher reported that wounds in the honey group healed faster, had superior histological results, and were more likely to have negative cultures at day 21.[53] However, 60% of the wounds in the silver sulfadiazine group became dry with eschar formation requiring surgical intervention, indicating that an insufficient quantity of silver sulfadiazine was applied to promote moist wound healing.[53] Another limitation is that bandaging, which may enhance healing by decreasing edema through incidental compression, was reported as being performed only for the honey group.[53] As is the case for most dressing studies, the patients and investigators were not blinded.[53]

The research team of Gore and Akolekar, in Mumbai, India, has persistently conducted well designed trials of improvised dressings for burns in tropical developing countries. Their facility began using boiled potato peel dressings in 1994, but because this choice proved to be adherent and painful, they switched to banana leaf dressings (BLs) in 1996.[54] In 2000, by Prasannababy, a nursing instructor, published a five-paragraph summary of a prospective randomized, controlled trial which found BLs superior to paraffin gauze on donor sites in Chennai, India.[55] In 2003, Gore and Akolelar published the results of their 1997 formal open controlled study of patients with comparable body area burns comparing BLs to boiled potato peels.[54] Both studies found that BLs were as effective as the comparator with significantly less pain overall, no pain at dressing changes, and significantly lower costs.[54,55] However, the BLs were autoclaved (sterilized using high pressure steam), which would not be possible in the impoverished rural setting.[54,55] In 2013, a large team of European researchers in Uganda reported excellent results with BLs as well.[56] These researchers confirmed that BLs require sterilization prior to use as a wound dressing because they are heavily contaminated with pathogens.[56,57]

Gore and Akolekar's facility adopted BLs as their standard for burn wounds, successfully treating over 2000 burn patients between 1997 and 2003.[54] However, in 2013 this facility

compared BLs with plastic surgical drapes on split thickness skin graft donor sites.[58] The donor site area was wrapped with a thick layer of gauze following the surgical procedure, allowing the patients to be blinded to the dressing choices until the first dressing change, which took place on about the seventh day.[58] The two improvised dressing choices were equally safe and effective, and the cost of each is minimal.[58] However, because the plastic drapes are completely non-adherent, virtually eliminating dressing change pain, Gore's facility now uses plastic surgical drapes, rather than BLs, on donor sites.[58]

Based upon case studies published by Toriyabe, et al., in 1999,[59] Takahashi, et al. conducted a prospective open-label non-randomized controlled trial to determine if patient outcomes would improve when ordinary plastic food wrap (PW) was used as the only treatment for stage III and IV pressure ulcers.[60] The 25 patients in the control group were treated with the then-current standard of care for elderly patients who had exceeded the 2 – 3 week dressing reimbursement time limit: ointments containing iodine, enzymes, or silver sulfadiazine (SSD).[60] The 24 patients in the experimental group only had their wounds covered with unsterilized PW, cut to allow exudate from autolytic debridement to escape.[60] A thin paper diaper protected the periwound skin in the more highly exudating wounds.[60]

Healing scores were significantly superior for the PW group at each assessment, reaching statistical significance at weeks 8 and 12.[60] Eschar formation was also significantly less likely in the PW group.[60] There was no difference in infection rates.[60] Maceration, noted in three study patients (not statistically significant), resolved quickly when the size and shape of the test dressing was adjusted and did not prevent wound healing.[60] This study was well designed with a simple protocol, and the subjects were well matched. Limitations include that the study was not blinded or randomized, and the sample size was small.

The studies by Toriyabe's and Takahashi's teams inspired Bito to lead a multisite study (15 hospitals in Japan) on stage II and III pressure ulcer patients comparing PW with following Japan's formal advanced moist wound therapy guidelines.[12] Outcome evaluations of the 64 patient RCT were performed by blinded wound experts using digital images.[12] Commercially available perforated PW, with no packing or ointment, was used to cover the wounds in the experimental group.[12] PUSH Tool (The Pressure Ulcer Scale for Healing) scores were calculated at two-week intervals for 12 weeks.[12]

Stage II ulcers healed slightly more quickly in the conventional therapy group, while Stage III pressure ulcers healed more quickly in the PW group.[6] Differences were not statistically significant.[12] The authors warn that the fact that the treatment could not be blinded could have influenced the care the patients received, because PW therapy is very popular in Japan.[12] Other study limitations were the small sample size, a high dropout rate, and the lack of wound closure as an outcome measure. This was a very well designed study with an experimental arm that could easily be mimicked in many developing country settings.

In response to Bito's study, PW therapy is approved for use in home health settings in the most recent (2016) Japanese Society of Pressure Ulcers' Guidelines.[61] PW is recommended as a pre-hospital burn dressing by the Australian and New Zealand Burn Association as well.[62]

Takahashi's team published results of a ten-year randomized controlled trial comparing PW with appropriate modern wound management for 142 Stage III and IV pressure ulcer patients in 2017.[63] The researchers noted that, to prevent infection, excess exudate was given a path to drain, either at the edge or through a slit or hole in the PW surface.[63] Also, large, very dirty wounds led to copious drainage from autolytic debridement, requiring dressing changes two to four times per day.[63] The primary outcome, wound surface area reduction, was evaluated by a blinded observer who evaluated digital photographs of the wounds at 4, 8, and 12 weeks.[63] Secondary outcomes (whose evaluators could not be blinded) included the PSST (Pressure Sore Status Tool*)* scores at the same intervals, and the incidence of adverse events.[63]

In this well designed study, PW was statistically superior to modern wound management in terms of both surface area reduction and PSST score reduction at all three time intervals.[63] Adverse events were lower in the PW group for all parameters except maceration, which was not clinically important.[63] All but one of the cases of maceration in both groups were on heel wounds.[63] Differences were not statistically significant for any adverse event.[63] The researchers concluded that PW is appropriate, even for dirty and heavily exudating wounds in frail elderly patients.[63]

All three choices described here have the potential of being safe and effective in the tropical hospital setting. However, the PW has the advantages that it has relatively consistent properties, and it does not require autoclaving, allowing it to be used in rural areas.[12,60] To verify that PW is inherently virtually sterile, researchers plated ten samples from a roll of PW that had been on an open shelf in a burns unit in Australia for several months onto agar plates and found zero growth after 72 hours.[62] For self-care, it is advantageous that PW dressings are completely non-adherent, and easy to prepare and change.[12,60]

Although PW is affordable, it is not currently widely available in rural areas of developing countries. However, the inner surface of a new thin plastic bag, such as those used to hygienically package fresh meat and to serve hot soup and rice, can mimic PW. Such bags, which are composed of the same non-toxic plastic as PW (Low-Density Polyethylene, or LDPE) are ubiquitous in rural markets throughout the tropics, and are generally exempt from plastic bag bans.[64–66]

Twelve plastic bags from tropical developing countries across the globe were Moisture Vapor Transmission Rate (MVTR) tested at body temperature by Illinois Instruments Inc. in anticipation of this study. Although the twelve bags varied in thickness and appearance, all had close to the ideal MVTR for moist wound management,[32] confirming that plastic bags are a reasonable surrogate for PW [data in appendices]. It is important to note that commercial thin-film adherent dressings (Tegaderm, Opsite) do not consistently provide an optimal moist wound environment because they have far higher MVTRs than PW.[32,67,68, see appendices for data tables]

Conclusion:

The studies from Japan and Australia demonstrate that PW is a safe, effective, acceptable wound dressing in temperate climates.[12,60,62,63] The lone study conducted in a tropical climate (India) found that sterile plastic surgical drapes are safe, effective, and acceptable on acute sterile (surgical) wounds in the tropics.[58] However, no published studies to date have confirmed that

plastic food wrap (or plastic bags) are a safe, effective, and acceptable wound dressing material for chronic wounds in a tropical environment.[27]

b. Rationale/Justification for this Study, and for the Methods Decisions

Sickle cell leg ulcers (SCLUs) are a challenging chronic wound type whose sufferers could benefit from a more economical, less painful, dressing option.[8,9] Only one of the studies involving occlusive plastic improvised dressings took place in a tropical environment, and this study tested a sterile drape placed in an operating theater on surgical wounds (donor sites).[58] Although theoretically autolytic debridement should keep wounds dressed with plastic bags clean, in practice there are concerns that wound infections could be problematic, because tropical climates are known to promote increased microbial growth.[19] Therefore, it is prudent to test the plastic bag dressing protocol under the guidance of health care professionals, where sufficient numbers of patients can be enrolled at a single site to answer the study questions definitively.

UHWI (the University Hospital of the West Indies) provides a rare intersection of sufficient research expertise to obtain accurate data, and a large number of SCLU patients living in a true tropical climate (air conditioning is not pervasive), allowing for partial testing of the ecological validity of improvised dressings. Validating the safety and effectiveness of affordable dressing materials would vastly improve treatment outcomes by winnowing out harmful self-care choices and supporting the beneficial choices. It would also empower patients, their families and lay health care providers by enabling them to implement effective treatments as first aid, prior to their arrival at an outpatient clinic or hospital.

Although there are as yet no specific proven topical treatments that improve SCLU healing, based upon one small study of SCLUs and results from venous leg ulcer studies, experts recommend moist wound dressings for SCLUs.[18,69] Moist dressings have been trialed at the Sickle Cell Unit in Mona, Jamaica, without proven benefit over usual practice. Honey, Unna boots, plastic wrap used circumferentially (a completely different technique from the one proposed here), and hydrocolloid dressings failed to produce superior results and/or were not accepted by patients, largely due to the warm climate. Because no moist wound healing method has been found safe, effective, and acceptable to the SCLU patients thus far, saline soaked gauze is the usual practice throughout Jamaica (as is the case throughout the world). However, comparing the improvised dressing only to saline-soaked gauze would virtually assure the impending obsolescence of the study results, because saline-soaked gauze does not stay moist and has been considered to be substandard care among wound management experts for over a decade.[18,32–34,70,71] Therefore, the only advanced moist wound dressing with a strong record of success when used in the tropics will be included as a positive control in this study.[72]

Polymeric membrane dressings (PMDs, PolyMem®, Ferris Mfg. Corp., Ft Worth, TX, USA) are unquestionably the advanced moist wound dressings with the most evidence to support their use in rural areas of tropical developing countries.[72–77] PMDs do not melt, break apart, or become adherent in a warm environment, and they are well tolerated in the tropics.[72,78,79] The continuous cleansing system that is an integral function of PMDs has been demonstrated to mitigate the problem of increased infections in the tropics.[72,79] PMDs also control inflammation and decrease

pain, two key influencers of healing in venous ulcers which may translate to sickle cell ulcers.[14,72,80] When used on venous leg ulcers, with or without compression, PMDs increased wound closure rates, sped healing, and decreased pain.[14,78] In addition, PMDs are among the very few advanced wound dressings mentioned favorably in the sickle cell literature.[7,9]

The literature review confirms that the two study dressings proposed here (improvised dressings composed of a small piece of food-grade plastic sealed with zinc oxide paste at the periwound, and PMDs) both show promise of being acceptable to patients, improving healing, and decreasing pain in the tropical environment, where previous alternatives have failed. Plastic wrap is gaining favor for wounds at Spanish Town Hospital, Jamaica. An SCLU patient in St. Catherine parish who chose to manage his wounds with the plastic bag protocol, and manages recurrences with PolyMem dressings, reports that both choices are less painful to use and more effective at closing SCLUs than usual practice (saline soaked gauze with papaya added when debridement was needed). Both of these alternative dressing choices are acceptable to the patient and his family.

Current usual practice and the advanced dressings are both relatively expensive, and neither use products available in the rural setting. The improvised dressing method is inexpensive and widely available, even in markets in impoverished rural settings. However, the least expensive wound is the one that is closed, and the advanced dressing may promote brisker wound closure. Additionally, the advanced dressing has pain-relieving properties which may enable patients to work and attend school.[72,80,81]

In summary, improvised dressings will be compared with usual practice and advanced dressings in SCLU patients in Jamaica in order to validate and promote a culturally relevant, inexpensive, effective wound management modality that can be easily utilized in every care setting.

Real world applicability of a study is enhanced if exclusion criteria are kept to a minimum. However, clear confounds should be avoided. Miller, et al., found that in young surgical patients, diabetes, cancer, kidney disease, hypertension, and abnormal BMI all significantly increased the chances of wound complications, while COPD, smoking, age, and HIV status did not.[82] Yang, et al., found that smoking, hypertension, age, diabetes, and obesity did not delay VLU healing, and that males were more likely to have delayed VLU healing.[83] In contrast, Lane, et al., found that smoking dramatically reduced pressure injury healing, and McDaniel and Browning found that smoking negatively impacts chronic wound healing by impairing neutrophil function and fibroblast activity; decreasing both white and red blood cell production; increasing carbon monoxide, hydrogen cyanide, and other toxic compounds; causing tissue hypoxia; and causing the release of catecholamines.[84,85] Smoking cessation programs led to improved wound healing.[84,85] Parker, et al., found that delayed venous ulcer healing was correlated with living alone, ulcer duration > 24 weeks, and age > 70 years.[86] A review of studies of venous leg ulcer management demonstrated that 12 weeks were sufficient to determine if a treatment was effective or not.[87]

2. Research Questions/Aim:

This study's primary purpose is to determine if an *improvised dressing*, made from inexpensive materials available for purchase in rural as well as urban settings, is a safe and effective, culturally and medically acceptable choice for managing sickle cell leg ulcers in a tropical climate. Three research questions will be addressed:

(1) Is the *improvised dressing*, consisting of a cut-to-fit new plastic bag sealed at the periwound with zinc oxide paste, safe and effective (see definitions, below) when compared with usual practice (saline-soaked gauze) and when compared with an advanced wound dressing (PMD), on sickle cell leg ulcers (SCLUs) in Jamaica?

(2) Does use of the *improvised dressing,* when compared with usual practice, improve the quality of life of patients (decrease pain, increase ability to engage in desirable activities, decrease wound-related materials costs, decrease time required to perform dressing changes, improve Wound QoL scores, and improve ASCQ-Me pencil-and-paper interview scores) with SCLUs in Jamaica?

(3) Is the *improvised dressing* culturally acceptable to health care providers, patients, and families for managing SCLUs in Jamaica?

The expected study outcome is improvised dressing superior effectiveness and quality of life, when compared with usual practice, without increased safety and acceptability issues.[13,59,60,62] The improvised dressing is likely to be the least expensive choice, with the added benefit of being available as first aid treatment throughout Jamaica. The advanced dressing is likely to be more expensive with respect to materials costs, although fewer dressing changes are anticipated and pain medication expenses are likely to be reduced. Based upon the review of the literature, no serious infections or other safety issues are anticipated for any group. However, to ensure that complications are not overlooked, in addition to the onsite researchers' vigilance, weekly wound photos will be assessed for complications (signs of infection, wound deterioration, or clinically relevant maceration) by two off-site blinded wound experts, Drs. Elizabeth Ayello and Dr. Joyce Black.

Definitions:

Sickle cell leg ulcer – a wound in a HbSS or HbSβ^0 positive patient, open greater than one month,[7] below the level of the knee excluding the plantar surface of the foot.

Closed wound – 100% epithelialized with no discernible scab or exudate production (paper napkin remains dry when lightly pressed against area, and no recurrence in the subsequent two weeks)

Safe – infection and other complications (healing-impairing maceration, keloid, and contracture rates) not statistically significantly higher than usual practice, with no major adverse events attributable to the method

Effective – ulcer closure rates or ulcer surface area reduction rates not statistically significantly lower than usual practice

Acceptable – average acceptability scores of 4 or higher on a 1 – 5 scale

3. Methods and Materials

a. Study design

This study will be a targeted-blinded (the off-site wound experts and the local physicians verifying wound closure and/or complications will be blinded to the randomization group), randomized controlled trial with three arms: (1) usual practice (negative control), (2) the improvised dressing, and (3) the advanced dressing (positive control). The expected outcome is improvised and advanced dressing superiority.

Although non-inferiority is an acceptable outcome for the improvised dressing, the review of the literature supports the expectation that it will outperform usual practice. This superiority study design eliminate the motive for the blinded evaluators to minimize differences between groups, biasing the results.[13] If superiority is attained, the results will be evaluated with intent to treat (ITT) analysis.

If superiority is not demonstrated, the data for the improvised dressing and usual practice dressing will be re-evaluated to assess for noninferiority.[13] Contrary to superiority trials where use of intention-to-treat is employed to protect against type 1 error, the appropriate approach for noninferiority trials is to use a per-protocol approach,[13] which, at worst, would exaggerate the differences between treatment groups, thereby yielding a more conservative estimate in the setting of a noninferiority trial.[13] Thus, only those patients completing treatment in the group to which they were randomized will be retained for any non-inferiority analyses (see appendix for further details).

b. Study population

Individuals diagnosed with sickle cell disease who have a SCLU and reside in the parishes of St. Catherine, St. Andrew, or Kingston parishes of Jamaica and respond to advertisements, recruitment phone calls, or flyers posted at the Sickle Cell Unit (SCU) clinic and UHWI prior to and during the enrollment period will be invited to participate in the study. Members of the UHWI surgical team will call all patients identified by the SCU as having had a SCLU within the past two years to invite them to participate in the study. Jamaican residents who otherwise qualify but who live outside the study area will be included only if they agree to provide their own transportation and faithfully attend all clinic visits.

c. Sample

Study participants must have HbSS or HbSβ^0 sickle cell disease, be between the ages of 13 and 70, and have a chronic SCLU, defined as a wound in a patient with sickle cell disease that has been open for at least one month and is below the knee, excluding the plantar surface of the foot. All SCLUs on a single patient will be dressed with the same dressing protocol. The largest ulcer at initial presentation is the study SCLU. If two or more SCLUs in close proximity join into

an enlarged ulcer during the first four weeks of the study, the sum of the initial areas will be considered the initial wound size for calculation purposes.

Decrease in SCLU surface area will be used to answer research question 1. Conducting a power analysis for this study is challenging because only one study of SCLUs has demonstrated a statistically significant outcome, and the effect size was obscured by high standard deviations, which is a common problem in studies of wounds.[8] Improvised plastic dressings similar to the study dressings were used in 49 chronic pressure ulcers in elderly patients, which are often slow to close, if they heal at all.[60] These two studies demonstrated a significant difference with confidence intervals of 99% with ~25 patients per group. Based upon these sample sizes and the Central Limit Theorem, it is reasonable to set the minimum sample size for this study at 30 patients per group,.[88,89]

d. Variables

Dependent Variables (measured weekly – tools and permissions in appendices):

1. Persistent wound pain (using the Faces Pain Scale – Revised (FPS-R))
2. Procedural (dressing change) wound pain
3. Amount of pain medication taken, including a total number of morphine equivalents plus non-opioid pain medications
4. Approximate time spent standing, or sitting with leg dependent without compression (estimated hours per week)
5. Patient overall quality of life (assessed with the ASCQ-Me Emotional, Pain, Social Functioning, Stiffness, and Sleep Impact Short Forms)
6. Patient wound-specific quality of life (assessed with the Wound QoL tool)
7. Materials costs (estimated, using lowest retail costs on Amazon.com for items not on the UWI price sheets)
8. Time spent performing dressing changes
9. Wound complication rates (e.g., wound infection, healing impairing maceration, wound deterioration)
10. Change in wound surface area (measured in cm^2 electronically using software that automatically corrects for skew, such as HealthEPix or WoundMatrix)[90]

Dependent Variables (measured one time, at graduation from study)

11. Wound closure time, in weeks (see definitions; verified two weeks later. Omit patients whose wounds did not fully close – they are included in 10., above.)
12. Acceptability of dressing choice – patient (5 point Likert scale and qualitative free response)
13. Acceptability of dressing choice – family member (5 point Likert scale and qualitative free response)
14. Acceptability of dressing choice – UHWI staff (5 point Likert scale and qualitative free response)

Independent Variables (documented at initial study visit):

1. Patient gender

2. Age of open wound prior to entrance into study (in weeks, patient/family report)
3. Previous ulcer treatments (if any)
4. Education level (in years)
5. Smoking or any use of nicotine (yes/no in past week)[84,85]
6. Mid-arm circumference (a surrogate for nutritional status)[91,92]
7. Initial area of SCLU in cm^2 (see methods for multiple adjacent SCLUs)
8. Initial depth of SCLU at deepest point, in cm
9. Anatomic location of SCLU
10. ASCQ-Me baseline scores (all measures – see appendices)
11. Social isolation (lives alone, without nearby support)[86]

e. Inclusion and exclusion criteria

Inclusion Criteria:

- Diagnosed with HbSS or $HbS\beta^0$ sickle cell disease
- Ages 13 – 70 years at study initiation (able to comprehend and give consent)[82]
- Males and females, pregnancy is not an issue
- Open wound below the knee, not including the plantar surface of the foot
- Wound open for longer than one month (defined as a chronic SCLU)
- Traumatic, spontaneous, or recurrent SCLU (all etiologies)

Exclusion Criteria:

- Patient younger than 13 years of age at study initiation
- Patient older than 70 years of age at study initiation
- Wound open for less than one month by conclusion of study enrollment period (acute wounds could be traumatic wounds unrelated to sickle cell diagnosis)
- Diagnosis of cancer, hypertension, or chronic renal failure[82]
- Diabetes (will screen for undiagnosed diabetes)[82]
- Active wound infection (evidenced by clinical signs of malodor, dark-colored or thick drainage, or significantly increased warmth at the periwound) which is not resolved by the conclusion of the study enrollment period
- Osteomyelitis (if osteomyelitis is suspected, an ESR will be drawn; > 70mm/h with high platelet levels and low serum albumin warrants a bone biopsy)[93,94]

- Hydroxyurea use (may be a confound because it reduces inflammation and negates much of the pathology of SSD – may choose to abstain for the study)[7,95]

f. Sampling

i. All eligible participants who consent to the study will be included. Participants will be randomized into one of the three groups immediately after the initial cleansing/debridement of their SCLU by the nurse using an electronic random number generator (an app). Waiting until the study dressing is to be applied to generate the random number will provide allocation concealment.

ii. Based upon previous studies and the Central Limit Theorem, an estimated 90 participants (~30 per group) may be required for the differences between groups to reach statistical significance.[12,23,88,89,96] Up to 120 patients will be recruited to allow for a 25% dropout rate. Based upon the literature review, pain, costs, wound size, and quality of life are expected to be significantly improved using the improvised dressings. However, because SCLUs are, historically, very slow to heal and often enlarge, complete wound closure is not an expected outcome for all patients.

g. Procedures for recruitment and consent

The study will be advertised using free community information channels such as church bulletins and radio outlets. Social media sites such as the CAIHR Facebook page will also be employed. Qualifying patients in the SCU database from up to two years prior to the study initiation will be called by the UHWI surgical team, alerting them to the dates for registering to participate. Flyers will be posted at the SCU in advance. Consent will be obtained by a member of the research team while the potential participant is waiting to be seen for wound care.

h. Data collection

The site for this study is the surgical clinic dressing area at the University Hospital of the West Indies (UHWI), Mona, Jamaica. The adjacent Sickle Cell Unit (SCU) will refer any SCLU patients to UHWI during the study period. UHWI is consistently well staffed with competent Jamaican health professionals. The UHWI surgical team will lead the study. Relatively few Jamaicans live or work in air-conditioned environments,[data in appendices] allowing the results from this out-patient population to translate to less developed tropical countries.

To ensure consistency, members of the research team will practice until they can demonstrate competency with all three dressing change procedures and with explaining the study forms prior to study patient recruitment.

Enrollment in the study will begin within two weeks of the day the Principal Investigator arrives at the Mona campus and will close 60 days later, or when a maximum of 120 patients have enrolled. All sickle cell positive patients presenting to UHWI with lower leg ulcers during the enrollment period will be screened for eligibility to enter the study. Each patient's data will be recorded for a total of 12 weeks, or until their SCLU has been closed for 2 weeks, whichever comes first.

Patients (and adult relatives of eligible patients under the age of 18) will have the study explained to them by one of the members of the UHWI surgical team. Questions will be addressed thoroughly. Families will be assured that if they choose not to participate in the study, the SCLU will be managed with usual practice. The patient (and a decision-maker of the family, in the case of a minor) must sign the consent for the patient to be enrolled in the study.

Immediately after consent is obtained, the study tools (Patient Data Collection sheet, Faces Pain Scale – Revised (FPS-R), ASCQ-Me, and Wound QoL) will be explained to the patient and family. Baseline persistent pain will be assessed using the Faces Pain Scale – Revised (FPS-R).

All of the initial independent variable data will be handwritten onto the patient's individual Study Data Collection Form upon enrollment in the study. The largest SCLU upon initial presentation is the study wound. All SCLUs will be measured for the first four weekly visits to UHWI. If two or more SCLUs in close proximity join during the first four weeks, the sum of the initial areas will be the initial wound size.

The SCLU(s) will be measured initially by placing two pieces of clear plastic on top of one another and tracing the wound edges. The plastic that came in contact with the wound(s) will be discarded and the plastic with the markings on it will be added to the patient's documentation so that the patient can be shown if the SCLU is becoming smaller at subsequent dressing changes. SCLU area will be measured in cm^2 electronically from a photo, using software such as HealthEPix or WoundMatrix.

Patients (with the support of their families) will be taught to evaluate and document persistent and dressing change pain, pain medication doses taken, time spent and supplies used at dressing changes, their activity, and their use of compression on a checklist-style Study Continuation Form daily. They will either provide the research team with their weekly summary and wound photo via WhatsApp, or they will attend the clinic weekly so that the research team can obtain this data. Two encrypted USB drives containing the data, including wound photographs, will be updated weekly on an alternating schedule and stored in a securely locked file in the UHWI surgical clinic dressing area, along with the paper study documentation.

Study patients will be randomized into groups 1, 2, or 3 immediately AFTER initial thorough wound cleansing/debriding by the nurse or physician. Randomization will be accomplished using an electronic random number generator (an app).

After a member of the UHWI surgical team performs the initial cleansing/debriding, the control group (1) will have their ulcer dressed as usually done at UHWI. Wounds are dressed with saline-soaked gauze, covered with dry gauze. One wrap of stretch gauze will hold the dressing in place. Patients will clean the wound by vigorously wiping with gauze soaked in homemade normal saline (1 tsp salt/500ml water bottle), center to edges, at each dressing change, unless already very clean. Clean wounds will simply be irrigated with normal saline at each dressing change. Patients experienced with using papaya for debridement of their ulcers may apply it only to the open wound, avoiding contact with the periwound, to remove slough or eschar. If patients observe green exudate, they are permitted to add one teaspoon of vinegar to their bottle of saline. Dressings in group (1) will be changed daily. The dressings will be soaked off if they become adherent.

After initial cleansing/debriding, patients in the improvised dressing group (2) will then have a thin layer zinc oxide paste applied to the dried periwound, carefully avoiding the open wound.[97] A piece of a clean new plastic bag (food-grade World Star 1 mil LD bags, or the equivalent, purchased from the Papine Market across John Golding Road from the University of the West Indies), cut slightly larger than the ulcer will be gently conformed to the moist wound contours and sealed onto the zinc oxide paste. The bag will be fenestrated with a small slit using a number 11 scalpel or clean scissors prior to placing it on the ulcer in order to allow excess fluid to escape. The edges of the slit will be approximated. Clean gauze will be placed lightly over the slit to capture escaping fluid. One wrap of stretch gauze will hold the dressing in place. Patients will be instructed to change the dressings daily, irrigating with normal saline at each dressing change.[6]

After initial cleansing/debriding, the advanced dressing group (3) will have a cut piece of a 4"x24" standard (pink) PMD roll large enough to extend at least 0.5 cm beyond all open and closed (inflamed or damaged) wound edges applied as per the Instructions for Use (the periwound is blotted dry, but the wound bed remains moist from the final saline rinse). One wrap of stretch gauze will hold the PMD dressing in place. The approximate open wound edges will be marked on the dressing backing. As per the manufacturer's instructions for use, patients will change the dressings when saturation reaches any of the wound edges, as indicated by a change in color on the backing of the dressing, visible through the stretch gauze. Routine rinsing will not be performed; the wounds will be rinsed at dressing changes only if visible loose debris is present.

All study patients will receive education about their illness and pain medication prescriptions per usual protocol. Patients are advised to use a compression wrap whenever their foot is dependent, as often as they are able to tolerate it. They will each be given a zipper-bag to contain and keep their wound management supplies clean.

Patients will be required to come to the UHWI surgical clinic dressing area in person weekly during the initial 4 weeks of study enrollment so that wound photos can be taken and the data for the ten dependent variables that are to be assessed weekly can be obtained. If their SCLU is clean without evidence of complications, patients/families who demonstrate the ability to take adequate pictures of their study SCLU with their mobile devices may instead send photos of their wound and their data collection sheets to the research team via end-to-end encrypted text messaging system (WhatsApp). All patients must agree to come to UHWI at least once per month to avoid being withdrawn from the study. Appointment times will include evenings and Saturdays to accommodate the schedules of students and employed patients.

Weekly, de-identified photographs will be sent by the Principal Investigator to be viewed by two blinded wound experts (Dr. Joyce Black and Dr. Elizabeth Ayello) off site. If the blinded experts, or anyone else involved in the study, expresses concern that a patient is exhibiting signs of possible infection, maceration that is delaying healing, or wound deterioration, a physician at UHWI or the SCU who is not otherwise involved in the study will be asked to evaluate that patient. The patient's dressings will be removed prior to this evaluation so that their treatment group will not be revealed to the physician (the evaluation by the physician is thus blinded to treatment group). If the physician determines that the patient's condition has not improved with the prescribed treatments (e.g., antibiotics), the patient will be withdrawn from the study. Any

patient who transitions out of the group to which they were randomized for any reason will receive usual treatment for their ulcer for the remainder of their 12 week study period.

When the treatment personnel at UHWI or the blinded remote observers state that the patient's wound appears to be closed, a physician at UHWI or the SCU who is not otherwise involved in the study will be asked to evaluate that patient. The patient's dressings will be removed prior to this evaluation so that their treatment group will not be revealed to the physician. Wound closure is defined as 100% epithelialized with no discernible scab or exudate production (a paper napkin blotting the area remains dry). Patients will be reassessed two weeks later to verify that the wound was truly closed and did not immediately recur.

Patients who are diagnosed with wound closure or have completed the 12 week study period will be taken aside privately and asked to rate the acceptability of their treatment using a 5 point Likert Scale. A family decision-maker will also be privately asked to rate the acceptability of the treatment. One of the research team members will enter this basic acceptability data for the patient and the family on the patient's Data Collection Tool. At that point, the patient will graduate from the study. However, patients and families will be instructed to return to UHWI for follow-up if a complication or recurrence develops. Any delayed complications (e.g., recurrence within 3 months) will be recorded on the patient's Data Collection Tool by the nurse or physician to whom the patient reports it.

As a token of appreciation from the research team and an incentive for patients to return for their study clinic visits, each participant will be presented with a 500JM phone card at the end of each of the three 4-week study periods.

All wound management supplies for all three groups will be donated. Shipping and handling fees will be paid by the Principal Investigator with funds from a Wound Healing Foundation grant. Tallies of supplies used at dressing changes will be priced using the cost of medical supplies purchased by the SCU to determine the estimated cost of the treatment supplies for each patient. The PMD rolls will be valued at $26.99US.[98]

The Principal Investigator will de-identify the data and compile it from the patient Data Collection Tools onto an Excel spreadsheet. This spreadsheet and the de-identified wound photographs will be backed up onto the Principal Investigator's second password protected hard drive via a secure internet connection at least weekly. Two encrypted USB drives containing the data, including wound photographs, will be updated weekly on an alternating schedule and stored in a securely locked file in Dr Venugopal's office in UWI Department of Surgery.

i. Statistical analysis

A consultant, Professor Sheryl Bishop, PhD, Senior Biostatistician at The University of Texas Medical Branch in Galveston, will undertake the analysis.

When all of the patients have completed the study, the remainder of the data from the de-identified Data Collection Tools will be transcribed into an Excel spreadsheet by the Principal Investigator. The data will then be evaluated by the biostatistician using the most recent version of SPSS. Groups will be compared with respect to each of the 14 dependent variables, taking into account any confounding from the 11 independent variables.

Results will be reported using descriptive statistics (means, modes, medians, frequencies), student's t test, and ANOVA with 95% CIs, using intent-to-treat.[13] If the improvised dressing does not attain statistical superiority to usual practice, 80% CIs will be calculated with drop-outs removed from the analyses to evaluate noninferiority.[13, Appendix: From Oczkowski SJW] Complications will be evaluated both individually and collectively by collapsing the pertinent columns.

Research questions (1) and (2) will be addressed by using analyses of covariance (ANCOVA) to determine if patients in the improvised dressing group (Group 2) had superior results (95% CI's will fall within *f*, the superiority margins) from usual practice (Group 1) or advanced dressings (Group 3), or, if this is not demonstrated, failed to vary significantly (80% CI's will fall within *f*, the inferiority margins) from usual practice (group 1) or advanced dressings (group 3) with respect to each of the dependent variables, controlling for relevant patient characteristics (the independent variables).

Research question (3) will be addressed with descriptive statistics across Likert items regarding endorsement of and concerns with use of the improvised dressing clinically or in future studies. Qualitative comments will be summarized across providers into content themes. Any differences between nurses, patients, family members, and physicians will also be explored and noted.

All health care providers at UHWI participating in the study will be surveyed to explore their concerns as well as their opinions about each dressing choice, using both qualitative open-ended and a quantitative question on a Likert scale. Results will then be shared with the participating clinical staff to provide them with the evidence concerning each of the three dressing protocols.

j. Data handling and record keeping

All study data will be transferred from written documents to the Principal Investigator's password protected electronic devices, de-identified, and then transmitted over secure internet connections to the backup hard drive in the USA. The paper study documentation and the two encrypted USB drives containing the raw data will be stored in a securely locked file in in Dr Venugopal's office in UWI Department of Surgery for a period of at least two years after the study has been published, after which they may be destroyed.

When all of the patients have completed the study, members of the UHWI research team will proofread the Excel spreadsheet with the de-identified data for transcription errors. This data will then be evaluated by the biostatistician using the most recent version of SPSS.

4. Ethical Considerations

This study will be approved by the Ethics Review Committee (ERC) at UWI and the Jamaican Ministry of Health (MOH) prior to its implementation. It will be listed on clinicaltrials.gov prior to the recruitment of the first study patient.

The patients, and available adult relatives of all eligible patients ages 13 to 18, will have the study explained to them by a member of the research team. Questions will be addressed

thoroughly. Patients and families will be assured that if they choose not to participate in the study, their SCLUs will be treated with usual practice. The patient, and in the case of a participant under the age of 18, a parent or guardian, must sign the consent for the patient to be enrolled in the study. Students will be accommodated after school or on a Saturday.

Time required to complete the weekly assessments for the study will create a burden for the study participants (approximately 30 minutes per week, total, and half a day once a month when patients come to UHWI in person for evaluation). However, dressing changes for the two comparator dressings are expected to be less painful and less time consuming than usual practice. In addition, all participants will be given study dressings and their wound care will be provided free of charge. Further, all study participants will be give a zipper bag of the dressing materials of their choice (gauze, plastic bags, or PolyMem; plus a roll of tape and a roll of stretch gauze) at the conclusion of the study.

This study is a collaborative project between the UHWI surgical team and the Benskin research team. In addition to her role as an independent researcher for tropical developing countries, as is stated in Ethics Checklist, Linda Benskin is an employee of Ferris Mfg. Corp., makers of PolyMem Dressings. This research study falls under her role as Charity Liaison for this company. The study has been designed with a high degree of rigor to help ensure that the results will not be biased as a result of this relationship.

The researchers anticipate that what is learned from this study can directly benefit the urban-dwelling Jamaican participants. In addition, many participants will benefit indirectly from the knowledge that their participation in the study can contribute to improving the lives of wound patients living in the rural areas.

SCLUs are often disabling, scarring, and exquisitely painful. The research literature suggests that both the improvised dressing and the advanced dressing can decrease pain. The advanced dressing has also been shown to decrease scarring. However, children ages 13 – 18 are an especially vulnerable population. They are included in the study because this is the peak age group for SCLU formation, and therefore they are the most likely to benefit if the results can be generalized to them.[15]

5. Limitations

Blinding is a challenge inherent to studies of wounds. Although the the healthcare professionals who will monitor and verify wound closure and complications (outcomes) will be blinded, it is not possible to blind the participants or the research team members, because they will provide the wound management in this study.

Despite the incentives to remain in the study (phone cards monthly and wound management supplies at the conclusion of the study), it is possible that there will be a substantial dropout rate, because it is easy for patients with SCLUs to become discouraged, and they may feel that they have derived the major benefits of joining the study after the first few weeks.

All of the published studies of improvised dressings describe wound care performed by health professionals based in urban hospitals or long term care facilities. Although this study will be conducted in a tropical outpatient setting, it too is being conducted by health care professionals in an urban area. Also, Jamaica is significantly more developed than many of the countries for whom the improvised dressing educational program may be beneficial. Therefore, this study may not uniformly generalize to rural areas of tropical developing countries, where health professionals are absent.

6. Acknowledgments:

The researchers would like to thank all participants in the study.

IX. INFORMED CONSENT FORM

A Test of the Safety, Effectiveness, and Acceptability of an Improvised Dressing for Sickle Cell Leg Ulcers in a Tropical Climate

Purpose and description:

The purpose of this study is to learn if there is a better way to manage sickle cell leg ulcers than what we have usually done. We will compare three wound dressings to learn more about the advantages and disadvantage of each dressing. We need detailed information to learn if any of the dressings are better than the others at decreasing pain, improving quality of life, speeding healing, decreasing wound problems, decreasing time required to perform dressing changes, and decreasing costs.

Procedures:

If you agree to be a part of the study, your wound will be cared for using *one* of three dressing methods. These are: usual practice, improvised dressings, *or* polymeric membrane dressings. Other new dressings that have been tried in the past in Jamaica have been disappointing to patients. We chose these two new dressing methods to try because they have worked well in other tropical countries. We do not know which of the three methods will be best for people with sickle cell leg ulcers in a tropical climate, like this one. That is why we are conducting this study.

You will not be permitted to choose which dressing method will be used. Instead, that choice will be determined randomly. Each person has an equal chance of being in any of the three dressing groups. *You may not change* to another group during the study. This is because we want to learn which method is best, and if people change from one method to another, it will be impossible to learn this. *After* you have completed the study, you will be given a packet of dressings of your choice. You can try them if your wound has not completely closed, or if you develop another wound.

You will need to come to the UHWI surgical dressing clinic for follow-up every week until you have mastered the dressing change procedure and can WhatsApp us the needed wound photos and information. You must manage your sickle cell leg ulcer at home exactly the way we teach you until it is closed, or until 12 weeks have passed. You must be willing to spend about 5 minutes every single day completing the Data Collection Tool, and about 30 minutes completing the quality of life questionnaires every single week. You can complete the questionnaires independently, or you can call us on WhatsApp and we will complete the forms for you by asking you the questions on the forms. If we do not receive your information every week, you will not be able to continue participating in the study. We will teach you to take high quality pictures of your wound with your mobile phone. If you are not able to WhatsApp us high quality wound photos and a photo of your completed Data Tool, at the end of the 4^{th} week and at the end of the 12th week – or sooner, if your wound closes – so that we can evaluate your wound and talk to you in person.

Risks:

If you agree to be a part of the study, your wound will be managed one of three ways, based upon your group. All three choices have been helpful to other people with wounds; none of them is likely to cause any harm. None of them are difficult to use. Sickle cell leg ulcers are painful, and we do not expect any of the choices to completely remove all pain. You are likely to have used usual practice in the past. This is a daily dressing change with saline-soaked gauze. The improvised dressing is a daily dressing change with a cut piece of thin plastic against the wound bed, with fluffed gauze over it. The polymeric membrane dressing looks like a thin sheet of foam rubber. The method chosen for your wound will be explained in more detail at your first study dressing change.

Benefits:

We are interested in decreasing pain, improving quality of life (such as, making it easier to sleep, socialize, and work), speeding healing, decreasing wound problems (like bad odor), decreasing time required to perform dressing changes, and decreasing costs to you and your family.

Right to withdraw or refuse to participate:
If you choose not to participate in the study, you can still take care of your wound just as you have in the past (most likely with "usual practice"). And, the UHWI staff will still help you care for your wound, just as in the past. Or, you can go to another clinic and try something different. You can also leave the study at any time. If you join the study, and then change your mind, it will be as if you never were a part of the study. No one will be upset with you if you decide not to participate or not to complete this study. You and your wound will be taken care of as if there were no research study.

Confidentiality:
The information we collect during this study (your completed forms and your wound photos) will be kept safe and private. When we evaluate and report the results, we will not include your name or any way for other people to know who the patients in the study were. We ask you to use WhatsApp to communicate with us because it is a secure, private way to send messages and pictures.

Compensation:
On weeks 4, 8, and 12, we will give you a JM$500 phone card as a small token of our appreciation for partnering with us in this study. When you complete the study, we will also allow you to take home a packet of study dressings, which can be different from the ones you were randomly assigned. You can use them if your wound has not completely closed, or if you develop another wound. There will not be any cash compensation.

Contact Details for Researcher/Principal Investigator:
If you have any questions regarding the research project later, that you did not think of now, please contact the principal investigator, co-coordinator, or research team at:
UWI, Department of Surgery, Radiology, Anaesthetics, & Intensive Care, Mona, Kgn 7
Dr. Benskin: lindabenskin@utexas.edu Tel: +1(512) 659-0812 Fax: +1 (425) 699-0812
Dr Venugopal: rvenu92@gmail.com Tel: (876) 927-1270 Fax: +(876) 970-4302

Rights as a Research Participant:
For independent advice on your rights as a research participant, please contact Dr. Gilian Wharfe, Chair of the Mona Campus Research Ethics Committee, Faculty of Medical Sciences, University of the West Indies, Mona, Kgn 7 Tel: (876) 970-4892 e-mail: mcrec@uwimona.edu.jm

Statement of DECLARATION:
1. I agree that this study has been explained to me and I have read it or had it read to me. I am signing this because, after careful consideration, I agree to participate in this research study.
2. I was given time to ask questions, discuss it with my family, and to think about my choice. All questions were answered to my satisfaction. I understand the study. I have been given a copy of this consent form.
3. Signatures:

_____	_____	_____
Signature of participant/respondent	Written name of participant	Date
_____	_____	_____
Signature of independent witness	Written name of witness	Date
_____	_____	_____
Signature of research team member	Written name of researcher	Date

IX. INFORMED ASSENT FORM

A Test of the Safety, Effectiveness, and Acceptability of an Improvised Dressing for Sickle Cell Leg Ulcers in a Tropical Climate

1. My name is _____.

2. We are asking you to take part in a research study because we are trying to find out if there is a better way to manage sickle cell leg ulcers than what we have usually done. We will compare three wound dressings to learn more about the advantages and disadvantage of each dressing. We need detailed information to learn if any of the dressings are better than the others at decreasing pain, improving your ability to participate in school and family activities, speeding healing, decreasing wound problems, decreasing time required to perform dressing changes, and decreasing costs.

3. If you agree to be in this study, your wound will be cared for using *one* of three dressing methods. These are: usual practice, improvised dressings, *or* polymeric membrane dressings. We do not know which of the three methods will be best for people with sickle cell leg ulcers in a tropical climate, like this one. That is why we are conducting this study. You will not be permitted to choose which dressing method will be used. Instead, that choice will be determined randomly. Each person has an equal chance of being in any of the three dressing groups. *You may not change* to another group during the study. This is because we want to learn which method is best, and if people change from one method to another, it will be impossible to learn this. *After* you have completed the study, you will be given a packet of dressings of your choice. You can try them if your wound has not completely closed, or if you develop another wound.

   You will need to come to the UHWI surgical dressing clinic for follow-up every week until you have mastered the dressing change procedure and can WhatsApp us the needed wound photos and information. You and your family must manage your sickle cell leg ulcer at home exactly the way we teach you until it is closed, or until 12 weeks have passed. You must be willing to spend about 5 minutes every single day completing the Data Collection Tool, and about 30 minutes completing the quality of life questionnaires every single week. You can complete the questionnaires with your family's help, or you can call us on WhatsApp and we will complete the forms for you by asking you the questions on the forms. If we do not receive your information every week, you will not be able to continue participating in the study. We will teach you and your family to take high quality pictures of your wound with your mobile phone. If you and your family are not able to WhatsApp us high quality wound photos and a photo of your completed Data Tool, you will have to come weekly. We do need you to come in to the UHWI surgical dressing clinic at the end of the 4^{th} week and at the end of the 12th week – or sooner, if your wound closes – so that we can evaluate your wound and talk to you in person.

4. If you agree to be a part of the study, your wound will be managed one of three ways, based upon your group. All three choices have been helpful to other people with wounds; none of them is likely to cause any harm. None of them are difficult to use. Sickle cell leg ulcers are painful, and we do not expect any of the choices to completely remove all pain. You are likely to have used usual practice in the past. This is a daily dressing change with saline-soaked gauze. The improvised dressing is a daily dressing change with a cut piece of thin plastic against the wound bed, with fluffed gauze over it. The polymeric membrane dressing looks like a thin sheet of foam rubber. The method chosen for your wound will be explained in more detail at your first study dressing change.

5. We are interested in decreasing pain, improving quality of life (such as, making it easier to sleep, socialize, and work), speeding healing, decreasing wound problems (like bad odor), decreasing time required to perform dressing changes, and decreasing costs to you and your family.

6. Please talk this over with your parents before you decide whether or not to participate. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes", you can still decide not to do this.

7. If you don't want to be in this study, you don't have to participate. Remember, being in this study is up to you and no one will be upset if you don't want to participate or even if you change your mind later and want to stop.

8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me at this telephone number _____ or ask me next time.

9. Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

_____	_____	_____
Signature of Adolescent	Written name of Adolescent	Date
_____	_____	_____
Signature of independent witness	Written name of witness	Date
_____	_____	_____
Signature of research team member	Written name of researcher	Date

IX. INFORMED CONSENT FORM

A Test of the Safety, Effectiveness, and Acceptability of an Improvised Dressing for Sickle Cell Leg Ulcers in a Tropical Climate

Purpose and description:
The purpose of this study is to learn if there is a better way to manage sickle cell leg ulcers than what we have usually done. We will compare three wound dressings to learn more about the advantages and disadvantage of each dressing. We need detailed information to learn if any of the dressings are better than the others at decreasing pain, improving quality of life, speeding healing, decreasing wound problems, decreasing time required to perform dressing changes, and decreasing costs.

Procedures:
If you agree for your child to be a part of the study, their wound will be cared for using *one* of three dressing methods. These are: usual practice, improvised dressings, *or* polymeric membrane dressings. Other new dressings that have been tried in the past in Jamaica have been disappointing to patients. We chose these two new dressing methods to try because they have worked well in other tropical countries. We do not know which of the three methods will be best for people with sickle cell leg ulcers in a tropical climate, like this one. That is why we are conducting this study.

You or your child will not be permitted to choose which dressing method will be used. Instead, that choice will be determined randomly. Each person has an equal chance of being in any of the three dressing groups. *No one may not change* to another group during the study. This is because we want to learn which method is best, and if people change from one method to another, it will be impossible to learn this. *After* you have completed the study, your child will be given a packet of dressings of their choice. They can try them if their wound has not completely closed, or if they develop another wound.

Your child will need to come to the UHWI surgical dressing clinic for follow-up every week until you have mastered the dressing change procedure and can WhatsApp us the needed wound photos and information.. They must manage their sickle cell leg ulcer at home (with your assistance) exactly the way we teach you until it is closed, or until 12 weeks have passed. Your child must be willing to spend about 5 minutes every single day completing the Data Collection Tool, and about 30 minutes completing the quality of life questionnaires every single week. They can complete the questionnaires with your help, or they can call us on WhatsApp and we will complete the forms for them by asking them the questions on the forms. If we do not receive their information every week, they will not be able to continue participating in the study. We will teach you to take high quality pictures of your child's wound with your mobile phone. If you are not able to WhatsApp us high quality wound photos and a photo of your completed Data Tool, your child will have to come weekly. We do need them to come in to the UHWI surgical dressing clinic at the end of the 4th week and at the end of the 12th week – or sooner, if their wound closes – so that we can evaluate their wound and talk to them in person.

Risks:
If you agree for your child to be a part of the study, their wound will be managed one of three ways, based upon their group. All three choices have been helpful to other people with wounds; none of them is likely to cause any harm. None of them are difficult to use. Sickle cell leg ulcers are painful, and we do not expect any of the choices to completely remove all pain. They are likely to have used usual practice in the past. This is a daily dressing change with saline-soaked gauze. The improvised dressing is a daily dressing change with a cut piece of thin plastic against the wound bed, with fluffed gauze over it. The polymeric membrane dressing looks like a thin sheet of foam rubber. The method chosen for your child's wound will be explained in more detail at their first study dressing change.

Benefits:

We are interested in decreasing pain, improving quality of life (such as, making it easier to sleep, socialize, and work), speeding healing, decreasing wound problems (like bad odor), decreasing time required to perform dressing changes, and decreasing costs to you and your family.

Right to withdraw or refuse to participate:
If you choose not to allow your child to participate in the study, they can still take care of their wound just as they have in the past (most likely with "usual practice"). And, the UHWI staff will still help them care for their wound, just as in the past. Or, you can take them to another clinic and try something different. They can also leave the study at any time. If your child joins the study, and then you or they change your minds, it will be as if they never were a part of the study. No one will be upset with you or your child if you decide not to participate or not to complete this study. Your child and their wound will be taken care of as if there were no research study.

Confidentiality:
The information we collect during this study (your child's completed forms and their wound photos) will be kept safe and private. When we evaluate and report the results, we will not include their name or any way for other people to know who the patients in the study were. We ask you and your child to use WhatsApp to communicate with us because it is a secure, private way to send messages and pictures.

Compensation:
On weeks 4, 8, and 12, we will give your child a JM$500 phone card as a small token of our appreciation for partnering with us in this study. When they complete the study, we will also allow them to take home a packet of study dressings, which can be different from the ones they were randomly assigned. Your child can use them if their wound has not completely closed, or if they develop another wound. There will not be any cash compensation.

Contact Details for Researcher/Principal Investigator:
If you have any questions regarding the research project later, that you did not think of now, please contact the principal investigator, co-coordinator, or research team at:
UWI, Department of Surgery, Radiology, Anaesthetics, & Intensive Care, Mona, Kgn 7
Dr. Benskin: lindabenskin@utexas.edu Tel: +1(512) 659-0812 Fax: +1 (425) 699-0812
Dr Venugopal: rvenu92@gmail.com Tel: (876) 927-1270 Fax: +(876) 970-4302

Rights as a Research Participant:
For independent advice on your child's rights as a research participant, please contact Dr. Gilian Wharfe, Chair of the Mona Campus Research Ethics Committee, Faculty of Medical Sciences, University of the West Indies, Mona, Kgn 7 Tel: (876) 970-4892 e-mail: mcrec@uwimona.edu.jm

Statement of DECLARATION:
1. I agree that this study has been explained to me and I have read it or had it read to me. I am signing this because, after careful consideration, I agree for my child to participate in this research study.
2. I was given time to ask questions, discuss it with my family, and to think about my choice. All questions were answered to my satisfaction. I understand the study. I have been given a copy of this consent form.
3. Signatures:

_____	_____	_____
Signature of parent	Written name of parent	Date
_____	_____	_____
Signature of independent witness	Written name of witness	Date
_____	_____	_____
Signature of research team member	Written name of researcher	Date