A comparative evaluation of a marine polysaccharide dressing and a carboxymethylcellulose dressing on subjects with lower extremity venous ulcers

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Version 4.0

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INVESTIGATOR ACKNOWLEDGMENT SIGNATURE

- I agree to conduct the study in accordance with the relevant, current protocol and will make changes in the protocol only after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct and supervise the investigation as described within.
- I agree to inform all subjects that the clinical products used in this study are being used for the purposes of an investigational study.
- I will ensure that requirements relating to obtaining informed consent in the guidelines for Good Clinical Practices (GCP), and 21 Code of Federal Regulations (CFR) Part 50 and Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.
- I agree to report to the Sponsor, IRB and/or Ethics Committee, according to the protocol, adverse experiences that occur during the course of the investigation in accordance with guidelines for GCP, and 21 CFR 812.
- I have read and understand the information in the protocol, including the potential risks.
- I agree to maintain adequate and accurate records in accordance with guidelines for GCP and 21 CFR 812.140 and to make those records available for inspection.
- I will ensure that an IRB compliant with the requirements of guidelines for Good Clinical Practices and 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in the guidelines for GCP, and the CFR.

I have received and reviewed this investigational plan. I will conduct the study as described.

_____
Investigator's name

_____ _____
Investigator's Signature Date

DOCUMENT HISTORY

VERSION	DATE	DESCRIPTION
Version 1.0	2-May-2019	Initial Release
Version 2.0	23-December-2019	1. Protocol edits requested by the site(s) 2. Updating the Serious Adverse Event form.
Version 3.0	20-June-2022	1. The sections for date were removed from the title page. 2. Medline Industries, Inc. was changed to Medline Industries, LP throughout the document. 3. The inclusion and exclusion criteria were modified in the synopsis and the main body of the protocol. 4. The dressings' change frequency was changed from twice weekly to at least once weekly. 5. The study duration was changed from 6-12 months to 6-60 months. 6. The "Investigator Acknowledgement Signature" page was modified to correctly include the abbreviations and remove the term "device". 7. The "Schedule of Activities" table was modified to include the changes in the study design. 8. The reference numbers of all the clinical products used in this study were included. 9. Product descriptions such as instructions for use and labeling information, and product images were removed from the appendix of the protocol. 10. The objectives and endpoints table in the protocol was modified so that the objectives and endpoints in the table are similar or identical

		to the objectives and endpoints stated in the synopsis. 11. The "Study Procedures and Assessments" section was modified per our current protocol template and changes in the study design. 12. The "Severity of Adverse Event" section was modified per our current protocol template. 13. The "Expectedness", "Adverse Event Reporting", and "Serious Adverse Event Reporting" sections were modified per our current protocol template. 14. An interim analysis was added in the "Statistical Considerations" section. 15. All the case report forms were removed from the appendix of the protocol. 16. Minor changes were made in the protocol regarding naming conventions, abbreviations, and wording used in our current protocol template.
Version 4.0	30-June-2022	1. One of the inclusion criteria was modified in the synopsis and the main body of the protocol.

1. PROTOCOL SUMMARY

1.1. Synopsis

Title: A comparative evaluation of a marine polysaccharide dressing and a carboxymethylcellulose dressing on subjects with lower extremity venous ulcers.

Study Description: Venous leg ulcers are lower extremity ulcers that develop due to sustained venous hypertension resulting from chronic venous insufficiency. Varicose veins, deep vein thrombosis, poor calf muscle function, arterio-venous fistulae, obesity, and history of leg fracture are some of the risk factors for venous ulceration. Numerous dressing types exist to treat these ulcers. This study will compare a marine polysaccharide (MPS) dressing (Opticell® Ag^+ dressing manufactured by Medline Industries, LP, referred to as MPS-Ag) to a carboxymethylcellulose (CMC) dressing (Aquacel® Ag Advantage dressing manufactured by ConvaTec, referred to as CMC-Ag), and will determine which dressing better manages these wounds with regard to wound size and periwound skin condition. Subjects will be randomized to receive either MPS-Ag dressing or CMC-Ag dressing.

Objectives: **Primary objective:** Evaluate and compare wound size changes in subjects when either MPS-Ag dressing or CMC-Ag dressing is used.

Secondary objectives: Compare (1) periwound skin condition, (2) subject perception of pain during dressing changes, and (3) dressing shrinkage.

Endpoints: **Primary endpoint:** Changes in wound size in subjects when MPS-Ag dressing or CMC-Ag dressing is used.

Secondary endpoints: (1) Evaluation of peri-ulcer skin assessment scale (PUSAS) score weekly for entire duration of study, (2) Subjective evaluation of subject pain perception during dressing changes using a numerical pain scale, and (3) Change in surface area of the dressing.

Study Population: Sixty-eight adult subjects with lower extremity venous ulcers will be selected.

Inclusion criteria will be:

- Males and females, 18 years or older.

- Subject is able and willing to comply with requirements of this trial protocol
- Subjects must be able to communicate effectively with study personnel
- Subject has lower extremity venous ulcer wound, as determined by the site Principal Investigator (PI).
- Subject has adequate lower extremity arterial circulation as determined by the site PI at the time of enrollment.
- Size of subject's wound is between $1cm^2$ and $100cm^2$.
- Duration of subject's wound is <52 weeks.

Exclusion criteria will be:

- Subjects who are pregnant, nursing, or planning to become pregnant during the course of the study.
- Subjects who have known allergies to any ingredient(s) in the clinical products used in this study including silver.
- Subjects who do not wish to use product(s) derived from shellfish.
- Subjects with substance use disorder within the past six months.
- Subjects with active infection and/or currently receiving antibiotic treatment for the wound included in the study.
- Subjects who are currently enrolled in another research study which includes investigational treatment and/or medication.
- Subjects judged by the site PI or sub-investigator to be inappropriate as a subject of this study.
- Subject has previous or current systemic disease(s) which, in the judgement of the site PI, is likely to interfere with the study. However, subjects with well-controlled diabetes mellitus (DM) (HbA1c < 8.5) shall be permitted.
- Subjects who receive any additional product or procedure/activity that could influence wound healing, such as chemical debridement, use of other wound cleansers, additional hydrogel or alginate wound products etc.

Phase:	Phase IV, Post-Market
Description of Sites/Facilities Enrolling Participants:	Multiple wound care centers

Description of Study Intervention:	Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized to receive either MPS-Ag dressing or CMC-Ag dressing. The wound will be cleansed with Skintegrity® wound cleanser, followed by application of MPS-Ag dressing or CMC-Ag dressing. Compression bandage (CoFlex® TLC Two Layer Compression Bandage system) will be applied over the dressing. The dressings will be changed at least once weekly but can be changed earlier by the clinician depending on the level of exudate. Wound assessments will be carried out weekly. The performance of both the dressings will be evaluated according to the study objectives.
Study Duration:	Six-to-Sixty months
Participant Duration:	Subject participation is intended to last for eight weeks after application of the dressings. Participant duration will begin upon obtaining informed consent and will end after eight weeks or earlier if the subject's wounds heal completely prior to eight weeks.

1.2 Schedule of Activities (SOA)

REQUIRED ASSESSMENTS & ACTIVITIES	Screening Visit Day 0	Initial Visit Day 1	Weekly visits (combined with dressing change visits) (Every 7 days ± 2 days)	Unscheduled Dressing change visits –	Final Visit (8 weeks from initial visit)[a,d]
Informed consent and screening form	X				
Wound assessment for eligibility	X				
Demographics and review of medical history		X			
List of medications taken by the subject		X	X	X	X
Application of new MPS-Ag or CMC-Ag dressings that will be compression wrapped[b]		X	X[c]	X[c]	
Pain assessment during removal and application of MPS-Ag dressing or CMC-Ag dressing, and dressing shrinkage evaluation		X[e,f]	X	X	X
Wound assessment (physical examination and infection evaluation)		X	X	X	X
Take wound photographs, record wound size and PUSAS score		X	X		X
Record analgesic use		X	X	X	X
Adverse event assessment		X----------X			

a: If the subject's wound heals prior to eight weeks, their participation in the study will be terminated.
b: Dressings will be changed at least once weekly but can be changed earlier by the clinician depending on the level of exudate.
c: MPS-Ag or CMC-Ag dressings will be removed, followed by application of a new MPS-Ag or CMC-Ag dressing, which will then be compression wrapped.
d: Dressings will be removed, without application of a new MPS-Ag or CMC-Ag dressing, on the final day and all the assessments will be carried out.
e: Pain assessment will be carried out only during application of MPS-Ag or CMC-Ag dressings on initial visit.
f: Dressing shrinkage evaluation will not be carried out in the initial visit.

2. INTRODUCTION

2.1. Background & Rationale

Venous ulcers account for 80% of lower extremity ulcerations; they develop due to sustained venous hypertension, resulting from chronic venous insufficiency. There are various risk factors for venous ulceration such as varicose veins, deep vein thrombosis, poor calf muscle function, arterio-venous fistulae, obesity, and history of leg fracture. Recurrent venous ulceration has been known to occur in up to 70% of those at risk. Severe complications arising from venous ulcers include cellulitis, osteomyelitis, and sometimes malignant change. There are various treatment options for venous ulcers such as conservative management including use of compression bandages, mechanical treatment, use of medications, and surgical options.[1,2,3]

There are numerous dressing types available that can be used to treat these ulcers. This study will compare a marine polysaccharide (MPS) dressing (Opticell® Ag^+ dressing manufactured by Medline Industries, LP, henceforth referred to as "MPS-Ag dressing") and a carboxymethylcellulose (CMC) dressing (Aquacel® Ag Advantage dressing manufactured by ConvaTec, henceforth referred to as "CMC-Ag dressing"), to determine which dressing better manages venous ulcers in subjects.

In this study, percentage reduction in wound size will be evaluated and compared between the two dressing types. Both the dressings will also be compared with regard to periwound skin condition, subject pain perception during dressing changes, and shrinkage of these dressings after their removal.

2.2. Clinical Products used in this study

2.2.1 Opticell® Ag^+ dressing (MPS-Ag dressing)

The MPS-Ag dressing used in this study has gelling action which helps to remove dead, damaged, and infected tissues from the wound, by trapping and removing them later at dressing change. It is designed to provide intimate contact with the wound for gentle healing. It also contains ionic silver which provides broad spectrum antibacterial protection. This dressing is currently marketed in the United States and is indicated for partial- and full-thickness wounds of all drainage levels, first and second-degree burns, diabetic foot ulcers, venous stasis ulcers, arterial ulcers and leg ulcers of mixed etiology, pressure ulcers, and surgical wounds. The reference number of this product is MSC9845EP. [4]

2.2.2 Aquacel® Ag Advantage dressing (CMC-Ag dressing)

The CMC-Ag dressing used in this study incorporates two technologies, Hydrofiber® technology and Advantage technology, to help eliminate the key barriers to healing that are exudate, infection, and bioburden. It can be used on chronic and acute wounds that are infected or at risk of infection with varying exudate levels. This dressing is currently marketed in the United States. The reference number of this product is 422299.[5]

2.2.3 CoFlex® TLC Two Layer Compression Bandage System

The CoFlex® TLC Two Layer Compression Bandage System (henceforth, referred to as "compression bandage") used in this study is used to manage venous disease. The first layer of dressing is soft foam which aims to wick away moisture. The second layer is composed of a short stretch of cohesive material that provides adaptive compression levels. It also comes with a nylon stocking that can be applied over the completed dressing for patient comfort and ease of movement under clothes and on bed sheets. The reference number of this product is AND7800.[6]

2.2.4 Skintegrity® wound cleanser

The Skintegrity® wound cleanser (henceforth, referred to as "wound cleanser") used in this study is a non-cytotoxic wound cleanser, that does not hurt healthy cells, and does not delay wound healing process. It is specially formulated with a gentle surfactant to allow thorough and gentle cleansing of wounds of all stages. The reference number of this product is MSC6008.[7]

MPS-Ag, CMC-Ag, compression bandage, and wound cleanser used in this study will be provided to the site Principal Investigators (PI) by Medline Industries, LP.

2.3. Risk/Benefit Profile

2.3.1. Potential Study Risks

Subjects may experience an allergic reaction to MPS-Ag dressing, CMC-Ag dressing, compression bandage, wound cleanser, or skin protectant. Therefore, to mitigate this risk, subjects will be screened for known sensitivity to MPS-Ag, CMC-Ag, or compression bandage dressings, and other commonly used dressings, as well as other clinical products used in this study. Additionally, subjects will be under the care of a physician, who will be able to appropriately address any potential reaction from the dressings.

2.3.2. Potential Study Benefits

Through the use of these dressings, subjects may experience faster reduction in wound size, improved skin quality of the periwound tissue, and reduced pain during dressing changes.

2.3.3. Assessment of Potential Risk/Benefit Profile

The use of these currently marketed dressings presents minimal risk, while offering the potential for benefits to the subjects enrolled in the study. Therefore, the risk-benefit profile for the study is favorable.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary: Evaluate and compare the change in wound size upon use of MPS-Ag dressing or CMC-Ag dressing.	**Primary:** Changes in wound size.	Reduction in wound size is an indicator of wound healing.
Secondary: 1) Compare the periwound skin conditions after use of an MPS-Ag dressing or a CMC-Ag dressing. 2) Compare subject perception of pain during dressing changes. 3) Compare shrinkage of MPS-Ag and CMC-Ag dressings.	**Secondary:** 1) Peri ulcer skin assessment scale (PUSAS) score will be evaluated weekly for entire duration of study. 2) Subjective evaluation of subject pain perception during dressing changes using a numerical pain scale. 3) Evaluation of dressing shrinkage by measuring change in surface area of the dressings after their removal.	1) Periwound breakdown can delay healing, worsen wound progression, and may also cause pain. Therefore, in addition to assessing the wound bed, it is also important to assess the periwound and surrounding skin.[8] 2) Evaluating subject pain perception during dressing change is also an indicator of ease of dressing change from the perspective of the subject. 3) Absorption of wound exudates decreases surface area of dressings. The ability of the dressing to absorb wound exudate, and yet maintain dressing size is an indicator of a high absorption capacity of the dressing.

4. STUDY DESIGN

4.1. Overall Design

This study is a multi-site, open-label randomized clinical trial comparing MPS-Ag dressing to CMC-Ag dressing and determining which dressing better manages these lower extremity venous ulcer wounds. Subjects will be randomized to receive either MPS-Ag dressing or the CMC-Ag dressing. The wound will be cleansed with the wound cleanser and designated dressing will be applied on the wound. It will then be wrapped with the compression bandage. The dressings will be changed at least once every week but can be changed earlier by the clinician depending on the level of exudate. There will be no home dressing changes. Wound assessments will be carried out weekly, such as change in wound size and PUSAS score evaluation. Subject pain perception during every dressing change will be recorded. If the clinician feels that peri-wound tissue requires protection, a skin protectant may be applied by the clinician or the clinical staff, per the facility's standard of care and clinician's discretion. Dressing shrinkage after removal of the dressings will also be determined. The Schedule of Activities in Section 1.2 describes the timing and sequencing of the events.

4.2. End of Study Definition

A subject's participation in the study may end at several critical points:

- Subject's wound heals, as determined by the site PI.
- Subject develops an infection at the wound site or any significant medical condition in the opinion of the site PI that precludes his/her continuation in the study.
- Subject has completed eight weeks of treatment.
- Subject withdraws from the study for any reason.

If the subject withdraws from the study, he or she will be replaced by another subject.

A clinical study report that has been approved by the Clinical Affairs Director will be issued following completion of the study.

5. STUDY POPULATION

5.1. Inclusion Criteria

A subject will be eligible to participate in the study if he or she satisfies *ALL* of the inclusion criteria below:

- Male or female, ≥18 years.
- Subject is able and willing to comply with requirements of this trial protocol.
- Subjects must be able to communicate effectively with study personnel.
- Subject has lower extremity venous ulcer wound, as determined by the site PI.

- Subject has adequate lower extremity arterial circulation as determined by the site PI at the time of enrollment
- Size of subject's wound is between 1cm^2 and 100cm^2.
- Duration of subject's wound is < 52 weeks.

5.2. Exclusion Criteria

A participant is ineligible for the study if he or she meets *ANY* of the criteria below:

- Subjects who are pregnant, nursing, or planning to become pregnant during the course of the study.
- Subjects who have known allergies to any ingredient(s) in the clinical products used in this study including silver.
- Subjects who do not wish to use product(s) derived from shellfish.
- Subjects with substance use disorder within the past six months.
- Subjects with active infection and/or currently receiving antibiotic treatment for the wound included in the study.
- Subjects who are currently enrolled in another research study which includes investigational treatment and/or medication.
- Subjects judged by the investigator or sub-investigator to be inappropriate as a subject of this study.
- Subject has previous or current systemic disease(s) which, in the judgement of the site PI, is likely to interfere with the study. However, subjects with well-controlled DM (HbA1c < 8.5) shall be permitted.
- Subjects who receive any additional product or procedure/activity that could influence wound healing, such as chemical debridement, use of other wound cleansers, additional hydrogel or alginate wound products etc.

5.3. Strategies for Recruitment and Retention

The site PI and/or sub-investigators and their staff regularly treat venous ulcer patients and will recruit eligible subjects from their practice. Each site will clearly and adequately convey that participation is voluntary, and that refusal to participate will not impact his or her medical treatment.

6. STUDY PROCEDURES AND ASSESSMENTS

6.1 Day 0 – Screening Visit and Informed Consent

6.1.1 Informed Consent

Prior to conducting study activities, written consent will be obtained from all participating subjects and documented on an informed consent form (ICF) that has been approved by an IRB/Ethics Committee. The ICF must be written in adherence to GCP and comply with all

elements required by FDA CFR 50.25 and ICH 4.8, state and local regulations, and additional elements relevant to specific study situations, (including a statement that Medline Industries, LP and authorities have access to subject records). A copy of the signed consent will be given to each participant.

6.1.2 Eligibility Screening

Potential participants will be screened for eligibility via a combination of the screening form and by a review of the potential participant's wound(s) and medical chart by the site PI and/or their staff.

If the participant has multiple wounds, the site PI will select the wound that meets the inclusion criteria. If more than one wound meets all the inclusion criteria, the site PI will choose the most clinically appropriate wound for the application of the dressings and will make a note of it in the Subject Screening form and the CRF.

6.2 Day 1 – Initial Visit

6.2.1 Demographics, Comorbidities, and Medication

Demographic information, subject co-morbidities, and a current medication list will be collected in order to understand if these variables affect the endpoints of wound size, periwound skin condition, and subject perception of pain during dressing changes. Information will be recorded on the CRFs.

6.2.2 Wound photograph and wound size measurement

During the initial visit, a member of the study staff will take photographs of the wound using a specialized wound camera with image analysis software (Insight® by eKare Inc.) and determine area and volume of the wound. The study staff will make every effort to obstruct identifiers such as tattoos/birth marks/scars in the wound images. In the event the camera or software malfunctions, manual measurement with a ruler will occur. Information will be recorded on the CRF.

6.2.3 Peri-ulcer skin assessment scale (PUSAS)[9]

Before application of the dressings, PUSAS will be used to measure the periwound skin condition. The instructions for use of assigning PUSAS score to the wounds will be provided. This score will be assigned to the wounds on which the dressings will be applied. Information will be recorded on the CRF.

6.2.4 Analgesic Usage

Since usage of analgesics will likely affect a subject's self-assessment of pain to dressing changes, analgesic usage will be recorded. This information will be recorded at the Initial Visit and all subsequent visits on the visit-specific CRFs.

After collecting all of the above information and data, the site PI or the qualified study staff will cleanse the wound, apply the designated dressing on the wound per the randomization schedule (see Section 8.2), and wrap it with compression bandage.

6.3 Dressing change visits - weekly and unscheduled

Subjects will have dressings removed at least once weekly (except on the initial visit) followed by application of new dressings. This will continue for eight weeks, from the initial visit, unless participation of the subject is terminated earlier as in section 4.2. The dressing change form will be completed at the initial visit and other subsequent dressing change visits. Additional information such as current analgesic, any new medication, irritation around the wound bed, and any abnormality in the wound status will be captured. If the clinician feels that the peri-wound tissue requires protection, a skin protectant may be applied by the clinician or the clinical staff, per the facility's standard of care and clinician's discretion, and will be recorded. The following information will also be recorded on the dressing change form:

6.3.1 Subject's perception of pain

A Numerical Rating Scale (NRS) will be used to measure perceived level of pain intensity on a numeric scale of 0-10, with 0 representing "no pain at all", and 10 representing "the worst pain ever possible".[10] Subjects will be asked to rate their current level of pain to dressing changes, such as removal of the dressing (except in the initial visit) and application of new dressing, at the wound site using this verbal pain NRS.

6.3.2 Infection evaluation

During dressing change visits, the wound site included in the study will be evaluated for development of any infection. In the event of a suspected infection, clinical staff will collect a wound culture. Should a subject develop an infection as confirmed by wound culture, this will be noted as an adverse event (AE) and his or her participation in the study will be terminated. Subject participation will also be terminated if they receive any antibiotic, prophylactic or therapeutic, for treatment of the wound site included in the study.

6.3.3 Dressing shrinkage evaluation

Dressing shrinkage, if any, will be evaluated by measuring surface areas of the dressings at the time of their application and during their removal.

6.4 Wound assessment visits – Weekly visits (Every 7 days ± 2 days) and final visit

Subjects must undergo dressing changes and wound assessments once every week. Analgesic(s) use will be recorded, and subjects will be asked to report any change in medication during their visits. Assessments carried out will be identical to those described in sections 6.2.2, 6.2.3, and 6.2.4, and sections 6.3.1, 6.3.2, and 6.3.3. The final visit will be the visit eight weeks from the subject's initial visit or whenever the wound is healed (whichever happens first). Dressings will be removed, and all the assessments will be carried out. Information will be recorded on the CRFs.

7 ADVERSE EVENTS

7.1 Definition of Adverse Event

In this study, an adverse event (AE) is any untoward medical occurrence related to the wound or treatment of the wound, including infection or a significant increase in pain during dressing changes.

7.2 Definition of Serious Adverse Event

The FDA definition of a serious adverse event (SAE) will be used in this study: An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions or,
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. All SAEs will be reported to Medline, regardless of potential relationship to the wound or treatment of the wound. SAEs will be reported to the reviewing IRB as necessary according to their rules.

7.3 Severity of Adverse Event

The severity of all AEs will be graded on a scale of one through five according to the Common Terminology Criteria for AE guideline, where each grade represents a unique clinical description based on this general guideline:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.

- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting activities of daily living involving self-care.
- **Grade 4:** Life threatening consequences; urgent intervention indicated
- **Grade 5:** Death related to AE

7.4 Relatedness of Adverse Event and Serious Adverse Event

- **Unrelated:** This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)
- **Possible:** This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the Investigational Product administration appears unlikely but cannot be ruled out with certainty.
- **Probable:** This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the Investigational Product.
- **Definite:** This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to the Investigational Product.

7.5 Expectedness

The site PI will be responsible for determining whether an AE or SAE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Expected AEs include a reaction or irritation at the wound site following application of the wound device or infection.

7.6 Adverse Event Reporting

The AEs will be recorded on the AE form by the study staff and reviewed by the site PI. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. Changes in severity will necessitate a new CRF to document the new level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

Non-serious AEs are to be reported to the study sponsor on a monthly basis for review or as agreed upon with the study sponsor and reported to the IRB per IRB reporting requirements.

7.7 Serious Adverse Event Reporting

The site PI shall complete a SAE Form and submit to the study sponsor as soon as possible, but in no event later than 48 hours after the investigator first learns of the effect. The site PI shall report the SAE to the reviewing IRB, if applicable, according to their reporting requirements. The study sponsor is responsible for conducting an evaluation of the SAE and shall report the results of such evaluation to the FDA and to all reviewing IRBs if applicable within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

For questions regarding this process or the event, you may contact your Medline clinical designee or the Medline Director of Clinical Operations:

Name: Julie Miller
Phone: 630-418-6891
E-mail: clinicaloperations@medline.com

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

A previous pilot study was conducted using a within-subjects design, applying both of the dressings described herein to two different wounds on the same subject, measuring wound reduction and other variables. In that study, the MPS dressing that was used led to a 40% reduction in wound size, whereas the CMS dressing led to a 33% reduction.[11] The data was used to determine the appropriate sample size for this study.

A power analysis using G*Power 3.1 for an independent samples t-test indicated that with the above reduction in wound sizes and a 10% standard deviation for each treatment, 68 subjects would be necessary to attain 80% power at a two-tailed alpha of 0.05, assuming a 1:1 assignment to the two dressing groups. A target of 80 subjects will be used in order to account for subjects' lost-to-follow-up and other scenarios that result in incomplete data.

8.2 Randomization

Local randomization will take place such that each site can randomize subjects into either group without the need for central coordination. Separate randomization lists will be generated for each site in blocks of four, in order to reduce the possibility of an imbalance in group assignment. Randomization lists will be provided in a forthcoming Statistical Analysis Plan (SAP) to be completed prior to study initiation.

8.3 Populations for Analyses

An evaluable population will be used for all analyses, with evaluable defined as any subject with valid initial visit and final visit wound size measurements.

8.4 Data Analysis

Descriptive statistics will be provided for the key endpoints, including measures of central tendency (mean or median, as appropriate), measures of variation (standard deviations, coefficients of variation) and 95% confidence intervals and interquartile ranges, as appropriate. Specifically, these measures will be calculated for:

- Changes in wound size
- Average percent periwound global score reduction
- Subject's pain rating during dressing changes
- Dressing shrinkage determined upon removal of dressings
- Proportion of subjects who develop an infection

The key assessment for differences in dressing performance will be based on the comparison of mean reduction in wound size for each dressing type. The specific details of the statistical testing will be provided in a forthcoming SAP. Comparisons of reduction in PUSAS score, subject pain ratings, and dressing shrinkage will also be made between the two dressing types, with specific details described in the SAP.

8.5 Interim Analysis

The most current version of PASS software Using PASS 2022 (Power Analysis and Sample Size Software (2022). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass) was used to estimate conditional power at n=46. It was determined that at n=46, a power of 80.65% could detect a mean difference of 7, with a non-inferiority margin of 0.5, at a target alpha-level of 0.05. The assumed population means are 40 and 33, with known standard deviations of 10 and 10. These results are based on one-sided t-test group sequential testing with 3 stages and boundary values calculated from spending functions. Since it is expected that 80% power has been achieved with n=46 cases, it is a reasonable time to perform in interim analysis to test for early efficacy and/or futility.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 Clinical Monitoring

The Clinical Research Associate (CRA) will confirm that the rights and well-being of subjects are protected, and that the reported trial data are accurate, complete, and verifiable from source documents. Moreover, the CRA will confirm the conduct of the trial by the PI, sub-investigator(s), and sites are in compliance with the protocol, GCP, and regulatory requirements as well as any applicable institution or IRB and federal or local processes. Monitoring will occur at minimum every two months, or more or less, depending on the enrollment during the study duration. It will occur more frequently if:

- The volume of data is large, there is a backlog of data to review due to unexpected issues, or there are quality issues with the data
- The site compliance with the protocol or compliance with expected ICH/GCP and regulatory requirements is lacking or there are continuing unresolved compliance issues
- There are unexpected AE/SAE or subject safety concerns noted
- There are any unexpected inconsistencies with study product management
- There is a request for more frequent monitoring by the site
- Any mutually agreeable situation as determined by the sites and Medline

The frequency of routine monitoring may be increased to a longer interval after three monitoring cycles if on-site situations support this change. CRA will discuss this with Medline Director or Clinical Manager and will inform the PI prior to implementation.

Monitoring activities will include subject eligibility, source data review, CRF completion verification, product accountability, site continued suitability, PI study oversight, compliance, and all general monitoring activities as outlined in FDAs Code of Federal Regulations and ICH/GCP guidelines that guide that activity.

Medline Industries LP may, on occasion, contract with external Clinical Research Organizations to provide CRA services and those CRAs are authorized to act on behalf of Medline Industries, LP.

It is expected that the site will be compliant with any institutional Standard Operating Procedures during the execution of the protocol and evidence of that compliance should be readily documented and verifiable by the CRA.

The CRA will generate an internal Medline Industries LP visit report that will be filed with the Medline Industries, LP trial master file and will provide the PI a detailed follow-up letter after each monitoring visit that will outline the completed monitoring activities as well as any identified areas of concern and the expected/applicable corrections needed. Medline

Industries LP, reserves the right to perform audit of the study activities – either routine or for-cause – as needed, and may also perform clinical monitoring audit as well.

9.2 Regulatory and Ethical Considerations

9.2.1 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the investigators, their staffs, and the Sponsor. Therefore, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor. All study data and study records will be managed and stored in accordance with the site's HIPAA compliant policies on data storage and security. All electronic transmission of data will adhere to HIPAA Security Rules.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB and regulatory agencies may inspect all documents and records required to be maintained by the investigators, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study sites will permit access to such records.

A master list linking subject numbers to subject name and medical record number will be maintained in a secure database (paper or electronic) by the site investigators. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for at least a period of two years, or longer if dictated by the reviewing IRB, Institutional policies, Sponsor requirements, or ICH/GCP and FDA requirements. The PI will agree to notify Sponsor of any intent to move or destroy these documents.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be maintained at the research sites on the CRFs. Copies of the CRFs, which will not contain any identifiable information, will be provided to the Sponsor for the purposes of data analysis. The study data entry and study management systems used by clinical sites and by Medline Industries, LP research staff will be secured and stored in an access controlled locked area (any paper forms) and password protected (electronic records). At the end of the study, all study databases that are not already de-identified will be de-identified and archived at Medline Industries, LP.

9.2.2 Safety Oversight

Given that this is a post-market study on dressings used in accordance with its labeling, there is minimal safety risk to participants. The site investigators treat patients with venous ulcers and are qualified to provide adequate safety oversight for the study. In the event there any AEs or SAEs, the site investigator will review them any make any necessary safety determinations as needed.

9.2.3 Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents of any kind (electronic, paper, etc.) should be completed in accordance with Good Documentation Practices (GDP) to ensure accurate interpretation of data. CRFs will be created for each subject. The CRA will verify the data entered into the CRF with the site source regardless of the type of source. The site will be responsible for developing a written process that ensures the CRA is able view the source data.

Data from the CRFs will be entered into an electronic spreadsheet via dual entry to assure no errors. Data will be transferred to and analyzed with SAS® for statistical analysis. SAS® allows for internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Medline Industries, LP will be responsible for overseeing final data analysis and confirmation of results.

9.2.4 Study Records Retention

Study documents should be retained until at least two years have elapsed since the formal discontinuation of the study intervention or as required by any applicable FDA guidelines or for a longer period if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the PI when these documents no longer need to be retained. The PI is required to notify Medline if the location of the stored documents is changed after it is defined at the time of the Close Out Visit at study end.

9.2.5 Study Discontinuation

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI, Sponsor, and IRB. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and Sponsor and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants as determined by AE review
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor and/or IRB.

9.2.6 Study Closeout

Upon completion of the study, Medline and/or its designees will notify the sites of closeout related procedures and will coordinate with the site the return of equipment and/or any unused product. Medline CRA will communicate closely with the PI and sub-investigators at that time point and will review all close out steps and materials. All study data, related study documents, and unused study product, will be returned to the Sponsor. Sponsor will provide the facility with a summary of the activities and findings after the final analysis of the data has been completed. The site will also notify the IRB that the study has completed.

9.2.7 Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication or any aspect of this trial will be disclosed and managed.

9.3 Protocol Deviations

It is the responsibility of the site investigators and study staff to use continuous vigilance to identify and report deviations on a routine basis. All deviations must be addressed in study source documents, and reported to Medline Industries, LP. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.4 Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
DM	Diabetes Mellitus
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Documentation Practice
HEOR	Health Economics and Outcomes Research
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form

ICH	International Conference on Harmonization
IFU	Instructions for Use
IRB	Institutional Review Board
LP	Limited Partnership
PI	Principal Investigator
PUSAS	Peri-ulcer skin assessment scale
SAE	Serious Adverse Event
SOA	Schedule of Activities

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