Effectiveness of MIRODERM® Biologic Wound Matrix in the Treatment of Hard-to-Heal Diabetic Foot Ulcers

(MIRODERM H2H DFU)

Protocol Number: 2016002

Sponsor: Miromatrix Medical, Inc.
10399 West 70th Street
Eden Prairie, MN 55344

Version: 1.1

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INVESTIGTOR PROTOCOL AGREEMENT PAGE

Effectiveness of MIRODERM® Biologic Wound Matrix in the Treatment of Hard-to-Heal DFUs

I have read the protocol specified below and as Principal Investigator agree:

- To assume responsibility for the proper conduct of the study at this site and supervise all testing of the device involving human subjects
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Miromatrix Medical Inc.
- To conduct the study in compliance with FDA regulations, and any additional requirements imposed by my institutional review board (IRB).
- To ensure that the requirements for obtaining informed consent from each subject are met and that no study specific procedures are implemented until the subject has given informed consent.
- Not to implement any changes to the protocol without written agreement from Miromatrix Medical Inc. and, as needed, prior review and written approval from my IRB except when necessary to eliminate an immediate hazard to patients.
- That I am thoroughly familiar with the appropriate use of the study device, as described in this protocol, and any other information provided by Miromatrix Medical Inc.
- That I am aware of, and will comply with, good clinical practice, applicable FDA 812 regulations and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Miromatrix Medical Inc. device and have been trained on their study related duties and functions as described in the protocol.
- Not to begin the study until the required approval is obtained from my IRB.
- Not to begin the study until a fully executed Clinical Trial Agreement is in place.

Investigator Signature	*Date*
Name	

STUDY CONTACT INFORMATION

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Study Synopsis

Protocol Number	**2016002**
Title	Effectiveness of MIRODERM® Biologic Wound Matrix in the Treatment of Hard-to-Heal Diabetic Foot Ulcers
Short Title	MIRODERM H2H DFU
Sponsor	Miromatrix Medical Inc.
Name of Product	MIRODERM® Biological Wound Matrix Fenestrated MIRODERM® Biological Wound Matrix Fenestrated Plus
Device Description *See IFU for complete details*	***MIRODERM Biological Wound Matrix*** MIRODERM is a non-crosslinked acellular wound matrix that is derived from porcine liver and is processed and stored in a phosphate buffered aqueous solution. MERODERM is available in a variety of sizes to be trimmed to meet the individual patient's needs and comes with or without fenestrations. MIRODERM is packaged in an inner sterile pouch and outer non-sterile pouch.
Intended Use *See IFU for complete details*	***MIRODERM Biological Wound Matrix*** This device is intended for the management of wounds including: • Partial and full thickness wounds • Pressure ulcers • Venous ulcers • Diabetic ulcers • Chronic vascular ulcers • Tunneled, undermined wounds • Drainage wounds • Surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence) • Trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) The device is supplied sterile and is intended for one-time use
Background	Estimates are 8% of the United States population are diabetic and up to 25% of these will experience at least one diabetic foot ulcer in their lifetime. Treatment of diabetic foot ulcers can cost $28,000 per episode. The presence of a diabetic foot ulcer increases chances of infection and future amputation. It is thus important to heal ulcers as expediently as possible. Ulcers refractory to treatment are of special concern and may prove responsive to treatment with MIRODERM Biologic Wound Matrix.
Study Center(s)	Up to 10 study centers will participate in this clinical trial.
Planned Sample Size	A minimum of 50 and not more than 65 subjects will be enrolled into this study.
Study Population	All patients who have at least one small to moderately sized diabetic foot ulcer and have been undergoing extended and unsuccessful treatment, as defined by failure of the wound to completely close over the previous 3 months and after application of at least 2 biological products.
Study Objectives	***Primary Objective***

	The primary endpoint will be the proportion of subjects who achieve wound closure by or at 12-weeks post treatment with MIRODERM. ***Secondary Objectives*** Some secondary objectives of this study include documenting the time course of wound healing and assessing changes in quality of life. The safety profile will be further characterized by tracking related adverse events.
Study Design and Procedures	This is a multi-center post-market, single-arm, prospective follow-up study ***Assessment and Roll-in Phase*** Subjects will be recruited by the treating physicians, screened for eligibility, invited to participate in the study and provide informed consent. The subject's demographics, medical history, co-morbidities and wound characteristics will be documented and the subject will complete a SF-36 quality of life questionnaire. Subject will be instructed on proper nutrition. Wound will undergo sharp debridement, be traced, photographed, and dressed per standard of care. Two tissue sections of at least 2mm will be retained for histological analysis. Subject will be fitted with and instructed on an offloading device. Subjects will return for MIRODERM treatment in two weeks. ***Treatment Phase*** On treatment day, wound will undergo sharp debridement, be traced, photographed and MIRODERM Biologic Wound Matrix will be applied. After treatment, subjects will be considered enrolled into the trial. Details of treatment will be documented. Subject will present weekly for the next twelve weeks. The dressing will be changed and may undergo further MIRODERM treatment if indicated. The wound will be traced and photographed. Physician will document their assessment on whether the wound is 100% closed. Subjects whose wound is completely closed at or prior to 12-weeks post-treatment, will be instructed to return 1-week following for a confirmation visit. Subjects whose wound is not assessed as closed by 12-weeks post-treatment, will have two tissue sections of at least 2mm collected, complete a quality of life assessment, and will then be discontinued per protocol. ***Confirmation Phase*** Subject will complete a quality of life assessment and have their wound area photographed. Physician will confirm the wound is still closed and the subject will be discontinued per protocol. If wound has reopened subject will return to the treatment phase.
Subject Participation	Subjects can be expected to reasonably participate in the study for a minimum of 9 weeks and a maximum of 15 weeks depending treatment course.
Inclusion Criteria	***To be included in this study, subjects must:*** Be 18 years old or older at time of initial visit Have Type I or Type II diabetes Be willing and able to sign an informed consent Have a neuropathic diabetic foot ulcer with the following characteristics: • Is greater than 1 cm^2 and less than or equal to 12 cm^2

	• Has failed to close following at least 2 treatments with a biologic • Has been present for 90 days or longer • Does not show signs of infection • Is full thickness (Wagner Grade I or II) • Located distal to the malleolus • Depth of less than or equal to 5 mm • No exposed capsule, tendon or bone • No tunneling, undermining or sinus tracts • Not between the toes Be willing and able to maintain required off-loading of affected limb Be willing and able to perform necessary dressing changes Have at least one of the following: • An Ankle-brachial index (ABI) ≥ 0.8 • $TcPO_2$ of ≥ 30 mmHg • A toe pressure of ≥ 50 mmHg
Exclusion Criteria	***To be included in this study, subjects must not:*** Be pregnant or be planning to become pregnant during the study Have had a Chopart's Amputation (or higher) Have a history of bone cancer of the affected limb Be undergoing dialysis Have active osteomyelitis or be receiving treatment for osteomyelitis Be diagnosed with unstable Charcot Foot on the affected side Have an HbA1c level of ≥ 12% within the past 90 days Have another ulcer within 2 cm of the study ulcer Be immunocompromised or at risk of immunosuppression as determined by the treating investigator Have a known collagen vascular disease or connective tissue disease Have received treatment of the study ulcer with a skin substitute product or topical growth factor within the past 4 weeks Be participating in another medical research study Have a sensitivity to porcine material
Schedule of Visits	1 Assessment and Roll-in (2-weeks prior to procedure) 2 Index Procedure 3 1-Week post-procedure (± 2 days) 4 2-Week post-procedure (± 2 days) 5 3-Week post-procedure (± 2 days) 6 4-Week post-procedure (± 2 days) 7 5-Week post-procedure (± 2 days) 8 6-Week post-procedure (± 2 days) 9 7-Week post-procedure (± 2 days) 10 8-Week post-procedure (± 2 days) 11 9-Week post-procedure (± 2 days) 12 10-Week post-procedure (± 2 days) 13 11-Week post-procedure (± 2 days)

	14 12-Week post-procedure (± 2 days) 15 Confirmation: 13-Week post-procedure (± 2 days) *All subjects will be offered a $25 gift card for completing weekly follow-up during the treatment phase.*
Study Duration	1 Year
Assessment Tools	Ankle Brachial Index HbA1c Monofilament test for neuropathy Photograph E-Z Graph Wound Assessment System Sf-36v2 Health Survey
Primary Endpoint	Proportion of subjects who have a closed wound at or before 12 weeks after the index procedure.
Primary Hypothesis	As an observational study, there is no formal hypothesis test. The precision of the estimate of the proportion of subjects who successfully close will be determined. Assumptions: • A minimum 50 subjects • A 95% Confidence Interval of the estimate • A 2-sided confidence interval • Using exact Clopper-Pearson estimation The Confidence Intervals (CI) at selected success rates are as follows: • @ 25%; CI = 25.4% Boundaries 13.8%-39.3% • @ 50%; CI = 28.9% Boundaries 35.5%-64.5% • @ 75%; CI = 25.4% Boundaries 60.7%-86.2% Thus, a sample size of 50 should allow for a reasonable estimate of treatment success at 12 weeks and for reasonable comparisons to historical controls.
Statistical Analysis	Descriptive statistics including but not limited to mean, standard deviation, frequency and percentages will be used to describe demographics, medical history, and characterize baseline variable as appropriate. A Z-test will be used to assess whether the proportion of subjects that were successful is greater than zero. Kaplan-Meier analysis will be used describe the survival curve assuming complete closure as the event of interest. A repeated measure ANOVA will be used to assess changes in, wound area and quality of life over time.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
DFU	DFU
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board

1 BACKGROUND

More than 23 million people (7.8%) in the United States are believed to have diabetes. Annually, 1 to 4 percent of people with diabetes develop a foot ulcer and that 10 to 25 percent of diabetic patients will have at least one foot ulcer during their lifetime (1) (2).

Diabetic foot ulcers (DFUs) are a chronic wound which commonly result from peripheral neuropathy and/or peripheral arterial disease associated with diabetes (3). The economic impact of DFUs as a subset of chronic wounds is considerable. An estimated annual $25 billion is spent on treatment of chronic wounds, and diabetes-related amputations cost approximately three billion dollars per year (2). In addition to treatment-related costs, disability and lost wages related to chronic wounds represents a heavy socioeconomic burden (2).

Standard care for treating DFUs address multiple issues and can vary between care providers. Common standard care considerations include wound debridement, pressure reducing strategies, restoring blood flow, maintaining a moist wound environment, wound infection management, and nutritional support (4). Supplemental treatment for chronic ulcers can include topical antimicrobials, hyperbaric oxygen treatment, cellular therapy, growth factors, and skin substitutes. Accelerated healing of chronic DFUs with skin substitutes can improve patient outcomes and mitigate the economic impact of DFUs.

MIRODERM® is a biologic, porcine liver derived, acellular wound treatment matrix. MIRODERM is FDA 510(k) cleared with an indication for the management of wounds including diabetic ulcers (K140510 and K143426). In addition to being porcine based, MIRODERM has several novel properties including an outer facing epithelial basement membrane with a wound facing open collagen matrix and an intact highly vascularized structure. Both of these are thought to improve the probability of epithelialization and cellular integration. Initial data suggest that MIRODERM can be effective in closing long open DFUs which have been refractory to standard of care and other biological products (5)

This clinical trial will rigorously document the ability of MIRODERM to treat hard-to-heal DFUs and further characterize the safety profile of this device.

2 STUDY DEVICE DESCRIPTION

MIRODERM is a noncrosslinked acellular wound matrix that is derived from porcine liver and is processed and stored in a phosphate buffered aqueous solution. MIRODERM is packaged in an inner sterile pouch and outer non-sterile pouch, in a variety of sizes to be trimmed to meet the individual patient's needs.

This device is available in fenestrated and fenestrated plus versions. Fenestrated plus has larger fenestrations than fenestrated. Although identical in composition, biologics, function, and indications, more fenestrated area allows for greater expansion and may facilitate greater exudate drainage.

MIRODERM® Biologic Wound Matrix is intended for the management of wounds including:

- Partial and full thickness wounds;
- Pressure ulcers;
- Venous ulcers;
- Diabetic ulcers;
- Chronic vascular ulcers;
- Tunneled, undermined wounds;
- Surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence);
- Trauma wounds (abrasions, lacerations, second-degree burns, and skin tears);
- Draining wounds.

3 RATIONALE

As a novel, highly vascular porcine derived biologic it is believed that MIRODERM wound biologic may heal wounds more successfully and in a shorter time. The rationale is to objectively demonstrate the clinical effectiveness of MIRODERM by empirically determining the proportion of wounds closed and fully describe the time course to closure.

4 OBJECTIVES OF THE CLINICAL INVESTIGATION

4.1 Primary Objective

The primary objective is to document the effectiveness of MIRODERM Biologic Wound Matrix, to close hard-to-heal DFUs at or within 12 weeks of initial treatment.

4.2 Primary Endpoint

The primary endpoint will be the proportion of subjects who achieve wound closure by or at 12-weeks post treatment with MIRODERM.

4.3 Secondary Objectives

Some secondary objectives include but are not limited to:

- Describe the time course to full wound closure
- Determine the subjects' quality of life score before and after treatment
- Characterize the safety profile of MIRODERM and the procedure
- Explore the histological characteristics of those who successfully heal and those who don't

5 RISK EVALUATION

5.1 Potential Risks to Study Patients

MIRODERM wound matrix is a cleared wound care product and will be used in accordance with approved indications and instructions for use (K140510 and K143426). As an observational, post-market study of a commercialized device for approved indications, the risk to a patient participating in this study is not fundamentally different than the risks this patent would encounter undergoing treatment with a porcine derived biologic wound matrix and not participating in this study. Thus, the only risk unique to this study would be inadvertent disclosure of protected health information.

There are risks, not directly associated with study participation, associated with treatment which may include but are not limited to:

- Sensitivity or allergic reaction to porcine material
- Infection
- Additional tissue damage during sharp debridement
- Cellulitis
- Osteomyelitis

5.2 Methods to Minimize Risks

Investigators will be licensed physicians in good standing. Trial centers and investigators will be selected on the basis of experience with DFU pathology, diagnosis and treatment. Investigators and study personnel will be trained on application of the product and the protocol.

The inclusion/exclusion criteria are consistent with the labeled indications and contraindications of MIRODERM Biologic Wound Matrix and will assure that only subjects who are appropriate for treatment with this product are enrolled.

Regular monitoring of the subjects' condition and tracking of adverse events (AEs) related to the device and trial will allow for the quick identification of potential problems with an individual subject as well as the entire cohort.

Again, MIRODERM Biologic Wound Matrix is a commercially available device being used as indicated. The risk to the patient participating in this study is not fundamentally different than that of a patient undergoing treatment for a DFU using a porcine derived biologic wound matrix and not participating in a study.

5.3 Potential Benefits of the Procedure

The potential benefit of treatment with MIRODERM Biologic Wound Matrix is closure of the refractory DFU and a reduction in the probability of infection, increased wound area and eventually amputation of the affected limb.

6 CLINICAL PROTOCOL

6.1 Study design

This is a multi-center post-market, single-arm, prospective follow-up study evaluating outcomes and efficacy of MIRODERM Biological Wound Matrix to treat hard-to-heal DFUs.

Assessment and Roll-in Phase

Patients who suffer from a persistent neuropathic DFU will be recruited from the investigators practice and network, screened for eligibility, invited to participate in the study and provide informed consent.

The subject's demographics, medical history, co-morbidities and wound characteristics will be documented and the subject will complete a SF-36 quality of life questionnaire. Subject will be instructed on proper nutrition.

The DFU will be treated by the investigator with sharp debridement, be traced, photographed, and dressed per standard of care; dressing will be changed daily by the subject. Two tissue sections of at least 2mm will be retained for histological analysis. Subject will be fitted with and instructed on an offloading device. Subjects will return for MIRODERM treatment in two weeks. At the discretion of the investigator, subjects may also be seen 1-week after initial visit; however, this interim visit is not required by the study and will not be documented.

Treatment Phase

On treatment day, subjects will have their wound debrided as necessary, photographed, assessed using the E-Z Graph Wound Assessment System and treated using MIRODERM. They will be asked to return weekly for dressing and wound assessment. After treatment with MIRODERM, subjects will be considered enrolled into the trial. Details of treatment will be documented.

Weekly, for up to 12 weeks, subjects will return, have their wound assessed for closure. As clinically appropriate, they may have their wound debrided and treated using MIRODERM. The wound will be photographed and assessed using the E-Z Graph Wound Assessment System and treatment details will be documented as applicable. The subject will receive a $25 gift card for attending the follow-up visit.

If wound has not closed, the dressing will be changed (subsequent to any needed treatment as described in the above paragraph) and the subject will return the following week. If the wound is healed subject will return for a confirmation visit one week later. If, after 12 weeks, the wound is not healed, subject will complete a SF-36 quality of life survey, two tissue sections of at least 2mm from the wound area will be collected and the subject will be discontinued from the study per protocol.

Confirmation Phase

Subject will complete a quality of life assessment and have their wound area photographed. Physician will confirm the wound is still closed and the subject will be discontinued per protocol. If wound has reopened subject will return to the treatment phase.

Subjects whose wound has been assessed closed will return for a confirmation visit. The wound will be assessed for closure. If the wound is still closed, the wound area will be photographed, the subject will complete a SF-36 quality of life survey and be discontinued from the study per protocol. If wound has reopened, subject will return to the follow-up phase at the appropriate post-treatment week continuing there until wound closure or through 12 weeks of follow-up as described in "Treatment Phase" above.

6.2 Sample Size, Subject Participation, and study Duration

This study will enroll up to 50 and no more than 65 subjects over 6 months. Single centers may continue to enroll until a maximum of 25% (13 subjects) of the planned minimum sample size or until, across all centers, the total sample size is reached. Subject participation will be approximately 9.0 to 15.0 Weeks from time of recruitment to study completion at 1) one-week following assessment of wound closer or 2) following 12 weeks of treatment. In both cases subjects will be discontinued from the study per protocol.

Subjects who do not complete the study per protocol may be exited from the study in the following manner:

- Subject presents with osteomyelitis or an infection of the study of the study DFU
- Subject voluntarily withdraws consent.
- Subject lost-to-follow-up
- Subject death

Subjects have the right to withdraw from the study at any time, for any reason or no reason, without jeopardizing their medical care.

6.3 Case Report Forms (CRF) and Subject Activities

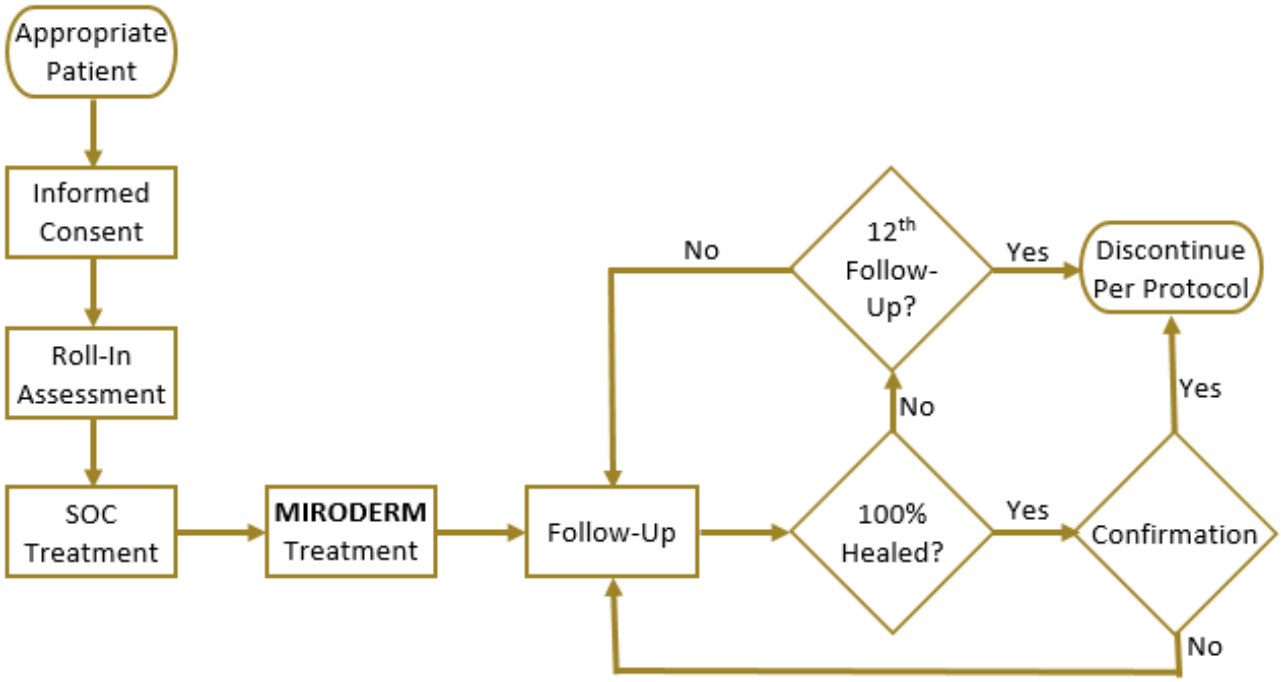
Table 1: Case Report Forms and Study Activities

Activity	**Study Visit**				
	Screening/ Roll-In	Treatment	Follow-up Visits	Final Follow-up	Confirm
Visit Timing	Week 1	Week 3	Weeks 4-13	Week 14	Week 15
Informed consent	**X**				
Inclusion Exclusion Criteria **[CRF]**	**X**				
Demographics, Medical Conditions, and Medical Co-Morbidities **[CRF]**	**X**				
SF-36 Health Survey **[CRF]**	**X**			**X**[1]	**X**
Wound Assessment and Treatment **[CRF]**		**X**	**X**	**X**	**X**
Subject Discontinuation **[CRF]**		**As Needed**			
Wound Tissue Sample	**X**			**X**[1]	
Wound sharp debridement	**X**	**X**	**As Needed**		
Wound Closure Assessment		**X**	**X**	**X**	**X**
Wound E-Z Graph assessment **[CRF]**	**X**	**X**	**X**	**X**	
Wound photograph	**X**	**X**	**X**	**X**	**X**
Wound Dressing and Care Instruction	**X**				
Subject Per Diem			**X**	**X**	**X**
Off-Loading Device Fitting and Instruction	**X**				

Activity	Study Visit				
	Screening/ Roll-In	Treatment	Follow-up Visits	Final Follow-up	Confirm
Visit Timing	Week 1	Week 3	Weeks 4-13	Week 14	Week 15
Nutrition Instruction	**X**				
MIRODERM Application		**X**	**As Needed**		
Adverse Event **[CRF]**		**As Needed**			
Protocol Deviation **[CRF]**		**As Needed**			

[1]For subjects who have not completely healed

6.4 Subject Study Flow Chart



6.5 Assessment and Roll-In Visit (Visit 1; Week 1)

6.5.1 Recruitment and Informed Consent

Male and female patients between 18 and 80 years old (inclusive) who suffer from a persistent neuropathic DFU will be recruited from the investigators practice and network. Patients will have a moderate sized ulcer that has not fully closed during the previous 3 months and who have received at least two attempts using biological solutions. Patients may present with multiple ulcers; however, only a single ulcer per subject will be selected for evaluation in the study protocol.

An assessment of the inclusion and exclusion criteria will be undertaken. All items assessed in the inclusion and exclusion criteria are tests or observations that would be known or obtained as standard of care regardless of the patient's participation in this study. Those patients which appear to be appropriate for the study will be asked to participate and undergo an informed consent procedure.

Patients will undergo the informed consent process. At this time, the study procedures, subject expectations and the approved Informed Consent Form (ICF) will be reviewed with the patient. The patient will be given an opportunity to discuss the study with the investigator, including any medical

aspect of their pathology and treatment. The patient will be encouraged to ask questions and will have all of their questions addressed to their satisfaction before deciding whether or not to be in the study.

6.5.1.1 Signing the Informed Consent Form

If the patient agrees to participate in the study, the patient will sign the consent form and will be provided with a copy for their records. ***Upon signing the consent form the patient will be considered an active subject in the study but not yet enrolled. The subject will be considered enrolled after treatment with MIRODERM***.

6.5.2 Inclusion criteria

To be included in this study, subjects must:

- Be 18 years old or older at time of initial study visit
- Have Type I or Type II diabetes
- Be willing and able to sign an informed consent
- Have a neuropathic DFU with the following characteristics:
    - Is equal to or greater than 1 cm^2 and less than or equal to 12 cm^2
    - Has failed to close following at least 2 treatments with a biologic
    - Has been present for 90 days or longer
    - Does not show signs of infection
    - Is full thickness (Wagner Grade I or II)
    - Located distal to the malleolus
    - Depth of less than or equal to 5 mm
    - No exposed capsule, tendon or bone
    - No tunneling, undermining or sinus tracts
    - Not between the toes
- Be willing and able to maintain required off-loading of affected limb
- Be willing and able to perform necessary dressing changes
- Have at least one of the following:
    - An Ankle-brachial index ≥ 0.8
    - $TcPO_2$ of ≥ 30 mmHg
    - A toe pressure of ≥ 50 mmHg

6.5.3 Exclusion criteria

To be included in this study, subjects must not:

- Be pregnant or be planning to become pregnant during the study
- Have had a Chopart's Amputation (or higher)
- Have a history of bone cancer of the affected limb
- Be undergoing dialysis
- Have active osteomyelitis or be receiving treatment for osteomyelitis
- Be diagnosed with unstable Charcot Foot on the affected side
- Have an HbA1c level of ≥ 12% within the past 90 days
- Have another ulcer within 2 cm of the study ulcer
- Be immunocompromised or at risk of immunosuppression as determined by the treating investigator
- Have a known collagen vascular disease or connective tissue disease
- Have received treatment of the study ulcer with a skin substitute product or topical growth factor within the past 4 weeks

- Be participating in another medical research study
- Have a sensitivity to porcine material

6.5.4 Health Survey

Subjects will complete a SF-36v2® Health Survey

6.5.5 Demographics, Medical Conditions and Co-morbidities

Investigator will document subject characteristics in the medical chart and on the appropriate case report forms including but not limited to:

- Demographics
- Current medical conditions
- Wound history and assessment
- Co-morbidities and general medical history

6.5.6 Wound Tissue Sample

Two tissue sections of at least 2mm will be retained from the debridement material for later analysis.

6.5.7 Wound treatment – Sharp debridement

The wound will be debrided, to the level of viable bleeding tissue, as necessary using sharp debridement. Other types of debridement (ultrasonic, enzymatic, larval, etc.) are not permitted.

6.5.8 Wound size documentation

The wound area will be documented using the E-Z Graph Wound Assessment System and photography.

6.5.9 Wound treatment – Dressing

Wound will be dressed per standard of care. Treatment dressing will include saline hydrogel to maintain moisture, a primary gauze layer and roll gauze as secondary covering. Subjects will be instructed on care of the wound and dressing and instructed to change the wound dressing every day during the Assessment Roll-In phase.

6.5.10 Off-Loading Device fitting and instruction

Subject will be fitted with an off-loading device and given instruction on use.

6.5.11 Proper Nutrition Instruction

Subjects will be given instruction on proper nutrition consistent with Cleveland Clinic's *Nutritional Guidelines to Improve Wound Healing* (2014, Cleveland Clinic) , and will be given a copy of the guidelines.

6.6 Treatment Visit (Visit 2; Week 3)

6.6.1 Wound Closure Assessment

Wound will be assessed for closure. If wound is closed subjects will receive no further treatment, have their wound size documented (per 6.8.2), and will be asked to return in 1-week for a confirmation visit.

6.6.2 Wound treatment – Sharp debridement

The wound will be debrided, to the level of viable bleeding tissue, as necessary using sharp debridement. Other types of debridement (ultrasonic, enzymatic, larval, etc.) are not permitted.

6.6.3 Wound assessment and size documentation

Wound will be assessed for gross dimensions and infection. If an infection is present an AE form should be competed and ***the subject will be discontinued from the study***.

The area of the wound will be documented using the E-Z Graph Wound Assessment System and photography.

6.6.4 Wound treatment – MIRODERM application and dressing

MIRODERM Biological Wound Matrix will be applied consistent with the IFU and wound will be dressed. An appropriate size of MIRODERM will be placed over the wound and, as needed, bolstered such that MIRODERM comes into contact with the maximum amount of wound surface. MIRODERM should be secured with Steri-strips, sutures or staples. Primary dressing shall have a non-adherent wound contact layer. Secondary dressing shall be roll gauze. No other biological material shall be used. ***Subjects will be considered enrolled into the study subsequent to treatment with MIRODERM Biologic Wound Matrix***. Treatment details will be recorded.

6.7 Follow-up Visits (Visits 3-14; Weeks 4-15)

6.7.1 Wound Closure Assessment

Wound will be assessed for closure. If wound is closed subjects will receive no further treatment, have their wound size documented (per 6.8.2), and will be asked to return in 1-week for a confirmation visit.

6.7.2 Wound assessment and size documentation

Wound will be assessed for gross dimensions and infection. If an infection is an AE form should be competed and ***the subject will be discontinued from the study***.

The area of the wound will be documented using the E-Z Graph Wound Assessment System and photography.

6.7.3 Wound treatment – Sharp debridement and MIRODERM application

If clinically indicated, the wound will be debrided, to the level of viable bleeding tissue, as necessary using sharp debridement. MIRODERM Biological Wound Matrix will be reapplied consistent with 6.6.4 and the IFU. Treatment details will be recorded.

6.7.4 Follow-up Stipend

Subjects will receive a $25 gift card at each follow-up. Distribution of gift card will be documented.

The following activities will be completed by subjects who present at the 12-week post-treatment visit and have a wound that is not fully closed.

6.7.5 Quality of Life Survey

SF-36v2 Health Survey will be completed.

6.7.6 Wound Tissue Sample

Two tissue sections of at least 2mm will be reserved from debridement material for later analysis. ***If debridement at the final follow-up is not medically necessary it should be omitted***.

6.8 Confirmation Visit (1 week after complete closure or Visit 15; Week 16)

6.8.1 Wound Closure Assessment

Wound will be assessed for closure. If wound is still closed subject will continue to 6.8.2 below. ***If it is determined that the wound is reopened***, subject will have wound assessed (6.7.2) and treated as needed (6.7.3). Subject will continue in the follow-up phase (6.7) until wound is closed or 12 weeks of follow-up have been completed.

6.8.2 Wound size documentation

The wound area will be photographed.

6.8.3 Quality of Life Survey

SF-36v2 Health Survey will be completed.

6.9 Study Exit

Subjects will be discontinued from the study per protocol. Under the following circumstances:

- Subject's index wound has been determined to be fully closed and remains closed at their 1-week follow-up confirmation
- Subject had completed their 12-week post-treatment follow-up and their index wound has not completely healed
- Subject presents with osteomyelitis of the study DFU or an infection of the study DFU
- Subject voluntarily withdraws consent.
- Subject lost-to-follow-up
- Subject death

When a subject is study exited, patients are no longer considered participants in the study and have no further obligations under the protocol. patients may undergo continued care as deemed appropriate by physician of record.

6.10 Description and Instruction for Case Report Forms, Assessments and Procedures

6.10.1 Informed Consent

The ICF will, in writing understandable to the subject, describe the study and its purpose. It will outline the potential benefits and the potential risks as well as what alternative procedures may be available. The confidentially of the subject's participation will be confirmed and the confidentiality of the subject's data and the study data will be described. Compensation and any anticipated expenses will be disclosed. Subject will be informed that any new findings which may affect their participation will be disclosed. As applicable circumstances under which the investigator or the sponsor may terminate the study will be explained.

6.10.2 Inclusion / Exclusion Criteria CRF

This form lists all of the criteria the subject must meet to be eligible for the study. ALL inclusion criteria must be met and NO exclusion criteria can be present for a subject to be eligible for the study.

6.10.3 Demographics, Medical Conditions and Medical Co-morbidities CRF

This will document subject's demographics including but not limited to, date of birth, gender, height, weight, BMI, ethnicity, current tobacco use and current alcohol use.

Current medical conditions and parameters, especially relative to inclusion and exclusion criteria, will be documented. This may include but is not limited to, HbA1c level, Ankle-Brachial Test, transcutaneous oxygen pressure test, (TcPO2), toe pressure test, and Monofilament Test.

History and current conditions of the DFU will be documented including but not limited to duration of ulcer, maximum height, length and depth, number of previous attempts to close with a biological solution and biological wound treatments previously used.

The subject's medical co-morbidities and history will document major system concomitant pathologies, drug allergies and current medication use.

6.10.4 Wound Assessment and Treatment CRF

This will document whether the wound is closed. To be closed there must be 100% epithelialization of the wound, no discernable exudate, and no further need for dressing.

Wound area and volume will be assessed by gross measurement of length, width and depth and assessed for infection.

With initial application during the treatment visit, and then when clinically indicated additional applications of MIROMESH will be documented including lot number, type, and size of MIRODERM Biologic Wound Matrix.

6.10.5 SF-36v2® Health Survey CRF

The SF-36 is a validated instrument which assesses an individual's current health status and heath related quality of life and can be used in health economic analysis. The SF-36 assess 8 sub-scales, vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The subscales may also be summarized in two measures assessing physical health and mental health. The SF-36 may be administered as a written survey or verbally.

6.10.6 Study Discontinuation CRF

This form will document when and the conditions under which a subject is exited from the study.

6.10.7 Adverse Event CRF

AE forms will document a description of the AE, onset and resolution dates, treatment, and investigator's assessment of severity and relatedness to the device.

6.10.8 Protocol Deviation CRF

This form will document the deviations from the study protocol. As needed it will document immediate corrections or corrective actions.

6.10.9 Ankle-Brachial Index

The ankle-brachial index is a noninvasive test of peripheral artery disease and an indicator of poor peripheral circulation. The ankle-brachial index test compares a person's blood pressure measured at the ankle with blood pressure measured at the arm. A low ankle-brachial index number can indicate circulatory problems. The ankle-brachial index should be determined at the time of initial assessment if there is no documentation within the past 90 days.

6.10.10 Hemoglobin A1C Test (HbA1C)

The HbA1C test measures the amount of glucose bound to hemoglobin in a red blood cell and is an indicator of blood glucose control over the previous two to three months. This test is used a screening test for diabetes. Values of less than 5.7% are normal, values of 5.75-6.4% are considered pre-diabetic and values of 6.5% or greater are considered diabetic. To be used as the inclusion criteria for this study, potential subjects should, within 90 days of Assessment and Roll-In, have a documented HbA1C value of 12% or less.

6.10.11 Transcutaneous Oxygen Pressure Test (TcPO2)

A TcPO2 test is a non-invasive test to quantify skin oxygenation and is indicative of cutaneous ischemia. TcPO2 levels above 30 mmHg are predictive for spontaneous healing while values of 10 mmHg or less are predictive of an unfavorable course of healing. To be used as the inclusion criteria for this study, potential subjects should, within 90 days of Assessment and Roll-In, have a documented TcPO2 value equal or greater than 30 mmHg.

6.10.12 Toe Pressure Test

A toe pressure test is a vascular test to confirm peripheral artery disease and limb ischemia. A toe pressure cuff is inflated above systolic artery pressure to occlude the vessels. The cuff is slowly deflated to reduce pressure. When blood returns to the vessels the pressure indicated is the toe pressure. To be used as the inclusion criteria for this study, potential subjects should, within 90 days of Assessment and Roll-In, have a documented toe pressure test value equal or greater than 50 mmHg.

6.10.13 Monofilament Test

A monofilament test is a non-invasive method to assess loss of protective sensation by determining if a person can detect pressure on their feet. Generally, a nylon monofilament which may be deformed at a pressure of 10 grams is pressed in an uneven cadence unsystematically upon 10 spots on an individual's foot. The individual is asked to signal when they feel pressure. The inability to detect pressure on 3 or more of the 10 tests will be considered to be positive for peripheral neuropathy. To be used as evidence for peripheral neuropathy, potential subjects should, within 90 days of Assessment and Roll-In, have a documented positive monofilament test.

6.10.14 Wagner Classification

The wound will be classified according to the Wagner Classification System as follows:

Table 2. Wagner's classification for foot ulcers (6)

Grade	Description
Grade 0	Pre- or post-ulcerative site
Grade 1	Superficial ulcer
Grade 2	Penetration into tendon or joint capsule
Grade 3	Involvement of deeper tissues, infection present
Grade 4	Gangrene of the forefoot
Grade 5	Gangrene involving more than two-thirds of the foot

6.10.15 Wound Tissue Sample

During initial debridement and with subjects whose wounds do not close after 12 weeks of follow-up, two tissue sections of at least 2mm from the wound area will be obtained. Each tissue sample will be placed into formaldehyde filled 5 ml plastic sample tubes provided. Using a standard "Sharpie" marker, each tube shall be labeled with subject number and date acquired. Tubes will be stored at room temperature until collected by the sponsor.

6.10.16 Wound width, length and depth assessment

Wound width and height should be measured to the nearest mm using disposable paper ruler. Wound depth should be measured at the maximum depth with reference to the plane of the skin's surface using a sterile cotton tipped applicator and measuring to the plane of the skin's surface.

6.10.17 E-Z Graph Wound Assessment System

This system will be used to assess inclusion exclusion criteria and to document changes in wound size over time. For the purposes of this study, the E-Z Graph® Wound Assessment Worksheet shall be considered a case report form.

Wound surface area measurement will be obtained via tracing using the E-Z Graph® Wound Assessment System. Whenever possible, tracings should be performed by a single person at the study site. The person(s) performing the tracing must be identified on the Delegation of Authority as having responsibility for this task. Measurement for study inclusion will be taken at the Assessment and Roll-in

Visit post-debridement and assessed by the investigator (or trained delegate). Further tracings will be completed at the Treatment Visit and again at each Follow-up Visit post debridement (where applicable). Trace the wound margin from the full-thickness, sharply debrided margins, eliminating any partial thickness involvement.

Tracing measurements will be performed as described below. Care will be taken not to lean heavily on the border or move the transparency while tracing.

1. Complete the information on the top of the E-Z Graph transparency entering the subject ID where Name is indicated and the Date. "Wound Location" and "TX Being Used" do not have to be completed.
2. Enter assessor's name on the appropriate line at the bottom of the text area and above the tracing graph.
3. Lay the E-Z Graph transparency on top of the wound with the center dot of the graph in the middle of the wound and the subject's head at the 12 o'clock position.
4. Use a fine-tipped permanent marker to draw around the full-thickness wound outline. Blue or black are the preferred marker colors for tracing. Trace only the open area of the wound.
5. Bend the lower right corner of the graph to peel off the backing, then align and adhere the graph to the E-Z Graph® Wound Assessment Worksheet. Use care as static electricity may suck graph to paper prematurely.
6. For assessing inclusion criteria, measure the surface area by counting each + symbol that lies mostly within the traced margin. If the center of the + symbol lies outside or directly beneath the outlined margin, do not count it. The number of squares counted will be the wound size in cm^2 and should be documented in the appropriate area of the Inclusion Exclusion CRF.
7. Make a photocopy of the completed E-Z Graph® Wound Assessment Worksheet and retain it in the subject's medical record. The original E-Z Graph® Wound Assessment Worksheet shall be placed in the E-Z Graph binder for collection and analysis by the sponsor.

In addition to the wound tracing, complete other information on the E-Z Graph Wound Assessment Worksheet as follows:

- STAGE
- WD BASE
- DRAINAGE AMT
- DRAINAGE TYPE
- PERIWOUND
- Yes-No determination
    - ODOR
    - ESCHAR/SLOUGH
    - UNDERMINING
    - TUNNELING

Note: completion of Length, Width and Depth are not necessary as thee values are collected on the wound assessment CRF. The back of the E-Z Graph® Wound Assessment Worksheet does NOT need to be completed.

6.10.18 Wound Photograph

Photographs will be used for qualitative visual documentation of changes in wound size and therefore the rigor of image acquisition will not be as great as that for quantitative measures. Photographs should be taken with a standard digital camera or phone with a minimum of 8 megapixels and auto focus. To

promote consistency within and among investigational sites, photography guidelines are described below.

Study photography guidelines are as follows:

1. Place a white or blue towel, paper, or sheet under the foot to serve as the background for the photo
2. Place the white ruled sticker labelled with the subject ID, and date, on the skin as near the wound as possible without covering the wound.
3. No other identifying information should appear in the frame.
4. The camera should be set to focus and flash automatically.
5. Position the camera parallel to the wound and approximately 12 inches from the wound.
6. Photographs should be saved on a secure location at the center and should be emailed on a regular basis to the sponsor. Sponsor will receive the photographs at clinicalaffairs@miromatrix.com.

6.10.19 Off-Loading Device: Fitting and Instruction

Subjects will be provided with offloading devices such as those listed below or similar:

- Ossur DH Offloading Walker®
- Ossur DH Offloading Post-Op Shoe

Subjects will be counseled on the importance of offloading for healing purposes. Investigators will instruct subjects to avoid weight-bearing on the study leg as much as possible and to use the prescribed off-loading device whenever ambulatory.

6.10.20 Nutritional Guidelines

Subjects will receive coaching on appropriate nutrition as well as foods that may impact wound healing consistent with the Cleveland Clinic's Nutritional Guidelines to Improve Wound Healing. As a nutritional reference, subjects will be given a copy of Cleveland Clinic's Nutritional Guidelines to Improve Wound Healing (see Appendix C) upon study enrollment.

7 STATISTICAL CONSIDERATIONS

As a prospective clinical outcome and survivorship study, there are no specific hypotheses to be tested. Data analysis may be conducted intermittently as needed or as requested by investigators without a power penalty and consist primarily of summary statistics and inferential statistics for changes in dependent measures over time.

Specific data analyses may include but are not limited to:

- **Demographics** and other pre-treatment characteristics will be summarized and characterized with appropriate descriptive statistics including error measures. Statistics may include mean, mode, median, range, inter-quartile range, minimum, maximum, frequency, cumulative frequency percentage and cumulative percentage. Results may be presented in a narrative and graphically.
- **Subject reported and dependent outcome measures** will be summarized and thoroughly characterized with the appropriate descriptive statistics including error measures. Statistics may include mean, mode, median, range, inter-quartile range, minimum, maximum, frequency, cumulative frequency percentage and cumulative percentage. Results may be presented in a narrative and graphically. Measures collected at multiple timepoints will also be analyzed using inferential statistics to assess changes over time, of special interest post-treatment changes from pre-treatment values. As appropriate a repeated measure ANOVA or Wilcoxon signed rank

test will be completed for each outcome measure. If a significant trend is identified, significance among time points may be further explored using the appropriate pair-wise comparisons. In all cases a p-value equal to or less than 0.05 will be considered significant. No corrections for multiple pair-wise comparisons will be made.

Missing data will be ignored in statistical calculations while using the appropriate n (sample size) for any given statistic or test.

Sample Size Justification: The precision of the estimate of the proportion of subjects who successfully close will be determined.

Assumptions:

- A minimum 50 subjects
- A 95% Confidence Interval of the estimate
- A 2-sided confidence interval
- Using exact Clopper-Pearson estimation

The Confidence Intervals (CI) at selected success rates are as follows:

- @ 25%; CI = 25.4% Boundaries 13.8%-39.3%
- @ 50%; CI = 28.9% Boundaries 35.5%-64.5%
- @ 75%; CI = 25.4% Boundaries 60.7%-86.2%

Thus, a sample size of 50 should allow for a reasonable estimate of treatment success at 12 weeks and for reasonable comparisons both to the literature and a history of not healing.

8 MONITORING PLAN

The investigators will allow onsite inspection of subjects' source documentation as requested by the sponsor or required by an IRB or regulatory authorities. Monitoring activities may take place at the trial center or any ancillary facility where study conduct takes place. The investigators will provide access to all source documentation and adequate work space. The investigators will be available to the sponsor, IRB or other regulatory authorities to discuss study issues as requested.

Data monitoring will be onsite and occur at the sponsor's discretion but at least annually. An initial monitor visit shall occur as soon as possible after enrollment of the first subject. As needed intermittent monitoring visits will be conducted to compare data entered into the database to all or an unsystematically selected subsample of the subjects' source documents. Monitoring efforts may be expanded if the sample suggests irregularities or for centers with robust enrollment. In all cases, monitor visits shall be conducted if excessive data anomalies are identified.

9 DATA MANAGEMENT AND RECORD RETENTION

Case report forms, paper or electronic, will be used to record satisfying inclusion and exclusion criteria, demographics, medical conditions and co-morbidities, the SF-36 Health Survey, wound assessment and treatment details, wound tracing and characteristics, and subject discontinuation conditions. As needed CRFs will be used to document AEs and protocol deviations. The subject data collected will be entered into a secure database by the clinician or designated staff. Subject data stored in the study database will be identified by the subject number. The unique number will identify the subject and will be included on all case report forms. Authorized representatives of the sponsor (e.g., monitors, auditors, the IRB) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, as needed, to monitor study conduct. By signing a written ICF, the subject is authorizing such access. The information obtained in this study may be published in scientific journals or presented at scientific meetings, however, the identity of individual participants will not be revealed

without specific written permission by the individual. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

The investigators will maintain all study records for at least two years following publication of the final study report.

Records to be maintained by the center include but are not limited to:

- IRB correspondence (including approval notifications) related to the clinical protocol, including copies of AE reports and annual or interim reports
- All versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s)
- Signed Clinical Trial Agreement, Investigator's Agreement(s), Financial Disclosure(s) and Protocol Agreement Page
- Curriculum vitae and medical license for Investigator(s)
- Training documentation for all study site personnel
- Signed ICFs
- Completed study worksheets (if used), signed and dated by investigator or delegated site personnel
- Source Documents not otherwise located in the subject's medical record
- Monitoring visit communications
- Copies of sponsor notifications of adverse effect information

The sponsor will maintain the following study records:

- IRB correspondence (including approval notifications) related to the clinical protocol;
- All versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s)
- Signed Clinical Trial Agreement, Investigator's Agreements and Financial Disclosures
- Curriculum vitae for Investigators
- Training documentation for all study site personnel
- Monitoring visit reports and communications
- Corrective and Preventative Action (CAPA) Plans, if applicable
- AE communications to sites
- Final clinical study report

Binders which may include subject identifying information shall be stored in a secure location at the study center. Subject confidentiality will be protected by the use of unique subject IDs in the electronic database. Subject names will not appear on study reports, publications, or other disclosures of clinical study outcomes.

Investigators will retain the specified records and reports for a minimum of two years after the investigation has been discontinued. Investigators may seek sponsor approval to transfer custody of the records to any other person or entity who will accept responsibility for them.

10 AMENDMENTS TO THE STUDY PLAN

Investigators will not modify, change or otherwise amend the protocol without prior written consent of the sponsor. As applicable, if a protocol amendment substantially alters the scientific validity of the study or affects the subjects' rights, safety, welfare, or their willingness to continue participation in the study, the subject should be re-consented on an updated and approved ICF. New procedures or processes which substantially alter the scientific validity of the study or affects the subjects' rights, safety, welfare, or their willingness to continue participation the study will not be implemented until approval has been granted by the reviewing IRB.

In emergency situations, Investigators shall disregard protocol requirements to ensure the safety, rights, or well-being of subjects.

11 DEVIATIONS TO THE STUDY PLAN

Investigators shall not deviate from the protocol without prior authorization by the sponsor except under emergency situations when necessary to preserve the safety, rights or well-being of subjects.

Deviations will be recorded on the appropriate form and include an explanation. Deviations or non-compliances that impact the rights, welfare, or safety of patients shall be reported to the sponsor and IRB as required.

If appropriate, corrective and preventive actions will be discussed by the sponsor, investigator, and/or the IRB to determine a suitable course of action

12 STATEMENT OF COMPLIANCE

This protocol has been developed will be run in accordance with the ethical principles set out in Declaration of Helsinki 2013. Further the study will be run in compliance with ISO 14155 (2nd ed) 2011, CRF Title 21, Part 50 and generally accepted standards of good clinical practice. Both investigators and sponsor will conduct this study in accordance with any applicable local, regional or federal laws and regulations.

Investigators will neither conduct procedures specific to the study nor collect subject data without prior approval of the IRB under whose jurisdiction the conduct of this study falls.

During study conduct, the investigators and the sponsor shall act in accordance with any further requirements as imposed by the IRB or other regulatory agency.

13 SUSPENSION OR TERMINATION OF THE STUDY

The study may be terminated at any time by the sponsor, with no further obligation to follow-up subjects. The study will be closed and the data will be archived according to the appropriate regulations.

14 ADVERSE EVENT AND SAFETY REPORTING

14.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject; it does not necessarily have to have a causal relationship with the device or the procedure. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or condition whether or not considered related to device or procedure.

Serious Adverse Event

A serious AE (SAE) is an AE that leads to 1 of the following conditions:

- Death
- Life-threatening illness or injury
- Serious deterioration in the health of the subject that results in 1 of the following situations:
    - Permanent impairment of a body structure or a body function
    - Medical or surgical intervention to prevent permanent impairment to body structure or body function
    - Inpatient hospitalization or prolongation of existing hospitalization
    - Fetal distress, fetal death, or a congenital abnormality or birth defect

14.2 Reporting of Adverse Events

For the purposes of this study, only events that occur after MIRODERM treatment can be considered AEs. Likewise, reportable AEs will be limited to AEs which are 1) definitely related to, or 2) likely related to, the study wound or treatment. Reportable events include but are not limited to:

- Cellulitis
- Osteomyelitis
- Wound recurrence
- A substantial increase in ulcer size
- Wound infection
- Debridement related AEs

AEs and follow-up information will be reported to the IRB according to the individual IRB's policies

14.3 Adverse Event Assessments

All AEs, which are 1) definitely related to, or 2) likely related to, the study ulcer or treatment will be documented on an AE form and assessed by the physician with respect to relatedness and severity.

Each AE record will include a description of the event, date of onset, date of resolution, severity, treatment as applicable, and relationship to study device. Each AE must be recorded separately.

Severity will be assessed using the following definitions:

Mild: Aware of sign or symptom, but easily tolerated

Moderate: Discomfort enough to cause interference with usual activity

Severe: Incapacitating with inability to work or do usual activity

Relationship to the study treatment or the study device will be assessed by the investigator using the following definitions:

Likely: A temporal relationship exists between the event onset and the study procedure or device, and appears with some degree of certainty to be related based on the event symptoms and the nature of the study procedure or device. It cannot be readily explained by the subject's clinical state or concomitant therapies.

Definitely: Strong evidence exists that the study procedure or device caused the AE. There is a temporal relationship between the event onset and the study procedure or device. There is strong mechanistic evidence that the event was caused by the study procedure or device. The subject's clinical state and concomitant therapies have been ruled out as a cause.

15 CLINICAL STUDY ADMINISTRATION AND INVESTIGATORS

15.1 Approval and Agreements

The sponsor and the principal investigator for this clinical research center shall agree to this document and any modifications. A justification for any modifications will be documented. Signing the signature page provided within this document will indicate approval and agreement with the protocol and methods of modifying the protocol.

15.2 Investigators

The investigators', qualifications and contact information will be updated and maintained by the sponsor. The name(s) and address(es) of other institutions involved in the clinical investigation as well as a complete list of monitors along with their contact information will also be maintained by the sponsor.

16 OTHER ETHICAL CONDUCT

16.1 IRB Approval

Prior to initiation of the study, the chairman or the recording secretary of the IRB charged with the responsibility of approving the investigation must sign an IRB approval form or letter, and a copy of the approval will be retained by the investigator and the sponsor.

16.2 Informed Consent

Prior to the performance of any study-specific procedures, the subject will have undergone a thorough informed consent procedure as described above (6.5.1 and 6.5.1.1).

The ICF includes all of the relevant elements currently required by Code of Federal Regulations Title 21 Part 50.

17 CONFIDENTIALITY

The information contained herein is provided to you in confidence and should not be disclosed to others, without written authorization from, except to the extent necessary to obtain informed consent from those persons to whom the device will be administered.

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Subject data will be stored in a computer database by the sponsor, maintaining confidentiality. Subjects in this database, will be identified by subject number. This number will identify the subject and will be included on all case report forms. Authorized representative of the sponsor (i.e. the monitor[s], the auditor[s], the IRB, and regulatory authorities) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, to the extent permitted by the applicable laws and regulations, and that by signing a written ICF and HIPPA waiver, the subject or the subject's legally acceptable representative is authorizing such access. Identities of individuals participating in clinical research will be kept as confidential as is possible within the law. While the information obtained in clinical studies may be published in scientific journals or presented at scientific meetings, the identity of participants will not be revealed.

18 REPORTING

After the completion of this study, the sponsor will analyze the data, generate a final report, and forward the report to all investigators. The investigators will submit a copy of the report to the reviewing IRB. The end of the study is defined as the last subject's last visit or at such time the sponsor decides to terminate the study. Final report will be completed within one year after the end of the study.

This information on this study and information on the investigators will be published on ClinicalTrials.gov as required by Section 801 of the Food and Drug Administration Amendments Act. By participating in this study investigators acknowledge and consent to this information release.

19 PUBLICATION POLICY

All data, results and any intellectual property derived from the data or results of the study are the property of the sponsor. The sponsor may use the data as they deem necessary, such as for submissions to governmental regulatory authorities, disclosure to other investigators and scientific communications. Sponsor and Study Principal Investigator will actively participate and engage investigators to actively participate in scientific communication production of aggregated study data at the sponsor's discretion and with sponsor review of the publication(s). The study sponsor will be responsible for determining

publication procedures and resolving authorship issues. Authorship may be determined by various measures, including contribution to the study design and enrollment rate.

The sponsor recognizes the right of the investigators to publish data and results derived from the participation of their center. However, prior to submitting for publication, presentation, using for instructional purposes, or otherwise disclosing results obtained from the study, the investigator(s) agree to allow the sponsor a period of at least 30 days to review the proposed publication or disclosure prior to its submission for publication or other disclosure. If the proposed publication/disclosure risks the sponsor's ability to patent any invention related to the study, the publication or disclosure will be modified or delayed for a sufficient time to allow the sponsor to seek patent protection of the invention.

This statement does not preclude the sponsor from having any editorial rights over the content of a publication or disclosure; however sponsor editorial comments shall be given no more weight than any other participant of the publication process.

Investigators may also request aggregate data summaries across all or a subset of all centers. These requests will be fulfilled at the sponsor's discretion. If the written contract for study conduct includes publication provisions inconsistent with this statement, then that contract's publication provisions shall apply rather than this statement

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