Clinical Outcomes After Treatment with Restrata™ Wound Matrix in Diabetic Foot Ulcers (DFU)

A Case Series of Initial Effectiveness and Safety Measures

Protocol Number: 17-RES-001

Revision: 01

Approval Date: 10/12/17

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PROTOCOL APPROVAL SIGNATURE PAGE

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Matthew MacEwan, PhD — Date
President / Chief Science Officer

Julie Cochran — Date
Chief Operating Officer

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1. PROTOCOL SUMMARY

Title	Clinical Outcomes After Treatment with Restrata™ Wound Matrix in Diabetic Foot Ulcers (DFU) A Case Series of Initial Effectiveness and Safety Measures
Protocol Number	17-RES-001; Revision: 01
Protocol Approval Date	10/12/17
Indications for Use	Restrata™ Wound Matrix is intended for use in the management of wounds, including: Partial and full thickness wounds, pressure sores/ ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled / undermined wounds, surgical wound (e.g., donor site/ grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), and draining wounds.
Acera Device	Restrata™ Wound Matrix
Study Purpose	Inform design of randomized controlled trial of Restrata™ Advanced Wound Matrix
Enrollment Size	Minimum of 30 patients
Study Design	Prospective, single armed, non-randomized study with direct assignment
Assessment Intervals	Baseline and weekly for up to 12 weeks with a closure confirmation visit within 2 weeks after complete closure has been first determined
Endpoint	12 weeks with closure confirmation visit 2 weeks thereafter

2. INTRODUCTION & PURPOSE

2.1. Background and Purpose

The process of wound healing requires a coordinated effort of cellular recruitment and tissue growth. Regenerative matrix materials have been used to promote this coordination and provide immediate wound coverage to minimize the risks associated with infection and fluid loss. An ideal material for these purposes would serve as a healing scaffold, limit infection risk, minimize inflammation, be readily available for use, and be conformable to diverse wound surfaces. [1,2]

Human autografts and allografts, animal-based xenografts, and fully synthetic materials have been used clinically with varying degrees of success. Autograft availability is limited by definition, and creates iatrogenic morbidity at donor sites. Allografts and xenografts eliminate the morbidity associated with autografts, but introduce additional risks of inflammatory response and disease transmission. Furthermore, host rejection of allografts and xenografts remains a concern in wound populations where the rate of immune disease has been reported as high as 23%. [3]

To support the infiltration of fibroblasts, the deposition of new collagen, and re-epithelialization of the wound surface, the wound matrix material should persist in the wound for at least three weeks. [4] The timing of wound matrix degradation is therefore critical, as the wound matrix should resist degradation until sufficient new tissue growth has occurred. The susceptibility of biologic wound matrix materials to enzymatic degradation leads to a resorption rate that is poorly controlled, risking the premature degradation of the wound matrix prior to sufficient wound healing. [5]

There remains a need for materials that minimize inflammation and promote complete wound healing. [6,7,8] Electrospun fibrous scaffolds may meet this need by mimicking the structure of native extracellular environment while enabling resident cells to perform their roles in the healing cascade. [9,10] The purpose of the following study is evaluate the initial safety and effectiveness of Restrata™ Wound Matrix in treating diabetic foot ulcers in human subjects, and to inform the design of a randomized controlled trial of Restrata™ Wound Matrix

2.2. Intended Use/Indications

The Restrata™ Wound Matrix is a sterile, single use device intended for use in local management of wounds. The Restrata™ Wound Matrix is a soft, white,

conformable, non-friable, absorbable matrix that acts as a protective covering for wound defects, providing a moist environment for the body's natural healing process to occur. Restrata™ is made from synthetic biocompatible materials and was designed to include a fibrous structure with high porosity, similar to native extracellular matrix. Restrata™ is a porous matrix with a defined rate of resorption that provides a scaffold for cellular infiltration and vascularization before completely degrading via hydrolysis. The device permits the ingress of cells and soft tissue formation in the defect space / wound bed. The device does not contain any human or animal materials or tissues.

Restrata™ Wound Matrix is supplied terminally sterile, in a single use double peel package in a variety of sizes. Restrata™ Wound Matrix may be fenestrated or meshed with a scalpel prior to application. Restrata™ must be fenestrated prior to use in any wound prone to exudate in order to permit effective exudate management. Contents of the package are guaranteed sterile and non-pyrogenic unless the package has been opened or damaged.

Restrata™ Wound Matrix is intended for use in the management of wounds, including: Partial and full thickness wounds, pressure sores/ ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled / undermined wounds, surgical wound (e.g., donor site/ grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), and draining wounds.

The benefits and risks of participation in this study will be described in the informed consent form.

3. STUDY DESIGN

Condition: Diabetic Foot Ulcers (DFU)

Aim: Inform design of randomized controlled trial of Restrata™ Wound Matrix

Number of Patients: 30

Number of Sites: Up to 8

Study Type: Interventional

Study Design: Allocation: Non-randomized
Endpoint Classification: Efficacy
Intervention Model: Direct assignment
Masking: Single Blind (Subject)
Primary Purpose: Treatment

Control Group: None (Utilize historical / published data on outcomes using standard of care)

Test Group: Treatment of DFUs with Restrata™ Wound Matrix

Primary Outcome Measures:

- Percent Wounds Closed [Time Frame: Baseline and weekly for up to 12 weeks]

  Wound healing will be assessed every week for 12 weeks or until the wound is completely closed, whichever occurs first. Persistence of wound closure will be verified via confirmatory visit within 2 weeks after complete closure has been first determined.

Secondary Outcome Measures:

- Decrease in Wound Area From Baseline [Time Frame: Baseline and weekly for up to 12 weeks]

  Wound area measurements will be made via tracing acetate every week for 12 weeks or until the wound is completely closed, whichever occurs first. Wound area will be verified via confirmatory visit within 2 weeks after complete closure has been first determined.

- Time to Wound Closure [Time Frame: Baseline through 12 weeks]

  The number of weeks until complete closure is first identified will be determined for each patient who has been deemed completely closed within the 12 week treatment period.

Tertiary Outcome Measures:

- Quality of Life- Odor reduction [Time Frame: Baseline (0 weeks), 4 weeks, 8 weeks, 12 weeks]

- Quality of Life- Itch reduction [Time Frame: Baseline (0 weeks), 4 weeks, 8 weeks, 12 weeks]
- Quality of Life- Visual appearance
- Number of reapplications / Size of units applied
- Incidence of adverse events (e.g. infection, etc.)
- Cost effectiveness / Economic model (Amount of product usage, length of treatment)
- Intraoperative notes / Ease of Use, Handling (Feedback on handling / ease of use and placement)
- Billing / Coding / Reimbursement information

4. PATIENT SELECTION

4.1. Inclusion Criteria

- Male or female age 18 or older
- Patient's ulcer must be diabetic in origin, located at least in part on the plantar surface and larger than 1cm^2 after the run-in period. Debridement will be done prior to randomization. Subject's informed consent for participating in this study, must be obtained prior to proceeding with sharp debridement
- Patients with Type 1 or Type 2 diabetes (criteria for the diagnosis of diabetes mellitus per ADA).
- Ulcer must be present for a minimum of four weeks before enrollment/randomization, with documented failure of prior treatment to heal the wound. A two-week run in period will precede enrollment/randomization in the trial to document the indolent nature of the patients selected
- Patient does not exhibit clinical signs / symptoms of infection upon gross observation (at least 3 of the following: pain, redness, purulence, exudate, temperature) or have been diagnosed with an active infection at time of screening
- Patient is willing to provide informed consent and is willing to participate in all procedures and follow up evaluations necessary to complete the study
- Patient has adequate control of diabetes, as demonstrated by one of the following within 30 days of screening:
    - HbA1c < 12%

  - Serum Creatinine < 3.0mg/dl
- Patient has adequate circulation to the affected extremity, as demonstrated by one of the following within the past 60 days of the first screening visit:
  - Dorsum transcutaneous oxygen test (TcPO2) with results ≥30mmHg, OR
  - ABIs with results of ≥0.7 and ≤1.5, OR
  - Doppler arterial waveforms, which are triphasic or biphasic at the ankle of affected leg

4.2. Exclusion Criteria

- Patients presenting with an ulcer probing to bone (UT Grade IIIA-D)
- Patients whose index diabetic foot ulcers are greater than 25cm^2
- Patient has an additional wound within 3cm of the study wound
- Patients not in reasonable metabolic control
- Patients with a known history of poor compliance with medical treatments
- Patients who have been previously enrolled into this study, or are presently participating in a clinical trial with DFU indications
- Patients with known or suspected local skin malignancy to the index diabetic ulcer
- Patients diagnosed with autoimmune connective tissues diseases
- Patients that have received a graft material on the study ulcer within the previous 30 days
- Patients who are pregnant or breast feeding
- Patients who are taking medications that are considered immune system modulator
- Study wound has closed > 30% over the two-week run-in period
- Patients with a known allergy to resorbable suture materials

5. STUDY CONDUCT

The schedule of events for this study is outlined in Appendix A.

5.1. Enrollment Procedures

Prior to enrollment, patients expressing an interest in participation will proceed with the inclusion/exclusion eligibility interview and informed consent process. An enrolled patient will be one who completes the eligibility interview, signs the Informed Consent form and receives the Restrata™ device.

5.2. Device Application / Follow-up Care Procedures

Please refer to Appendix B for a list of supplies that will be provided by Acera for wound assessments / follow-up care procedures.

1) WOUND BED PREPARATION:

- Review patient's medical history and physical examination.
- Complete the Informed Consent process.
- Perform gross observation of the wound site for evidence of infection.
- Conduct all pre-application Quality of Life assessments and surveys.
- Prepare the wound bed using standard methods to ensure it is free of exudate and devitalized tissue. An initial excision or debridement of the wound may be necessary to ensure the wound edges contain viable tissue.
- Wait for any bleeding to stop before applying Restrata™ Wound Matrix.
- Cleanse the wound thoroughly with sterile saline prior to application of Restrata™ Wound Matrix.

2) PREPARATION OF RESTRATA™ WOUND MATRIX

- Measure the wound area and select the appropriate size sheet of Restrata™.
- ***Heavily fenestrate Restrata™ with a scalpel prior to application***. Restrata™ must be fenestrated prior to use in any wound prone to exudate in order to permit effective exudate management.
- Restrata™ is packaged in a nested pouch configuration. Peel open the outer foil pouch starting from the chevron sealed edge. The inner TyVek® pouch is sterile and may be placed on the sterile field.
- Rinse surgical gloves, if necessary, to remove any glove powder prior to touching the product.
- Restrata™ can be cut to the desired shape in a wet or dry state. In order to increase pliability of the product, hydrate Restrata™ in warm, sterile, hypertonic solution (i.e. saline, water, etc.) for a minimum of 1 minute.

3) APPLICATION OF RESTRATA™ WOUND MATRIX:

- Apply Restrata™ with either side towards the wound bed, and position to completely contact the entire surface of the wound bed and extend slightly beyond wound margins. Restrata™ can be repositioned as necessary.
- Securely anchor Restrata™ Wound Matrix as needed with suture or Steristrips.
- Apply a non-adherent primary wound dressing over the Restrata™ Wound Matrix. ***No topical treatments of any kind should come into contact with Restrata™ after it is placed.***
- To prevent dislodgement of device, apply appropriate secondary dressing or compression to maintain dressing adherence (e.g., multi-layer compression bandage system, or other appropriate dressing), manage the wound exudate, keep the Restrata™ Wound Matrix moist, and keep all layers securely in place. The optimum secondary dressing is determined by wound location, size, depth and user preference.
- To ensure off-loading, each patient will be fitted with an identical CAM boot provided by Acera to encourage standardization of wound treatment. The investigator may prescribe a CAM boot other than the one provided by the sponsor, without being considered a protocol deviation, but only if the investigator determines the provided CAM boot is insufficient for complete off-loading of the wound area.
- Discard any unused pieces of Restrata™ Wound Matrix.

4) DRESSING CHANGES:

- Change the secondary dressing as appropriate. Frequency of secondary dressing change will be dependent upon volume of exudate produced, type of dressing used and the clinician's need to inspect the wound bed for signs of infection or healing.
- ***Unless infected, the following dressing types should not be applied as part of dressing changes: hydrocolloids, foams, alginates, or silver-impregnated dressings.***

5) WOUND ASSESSMENT:

- Carefully assess the wound and record healing progression such as wound dimensions, wound depth, signs of infection, description of exudate present, and wound bed characteristics.
- Evaluate the amount of Restrata™ Wound Matrix remaining in the wound and describe the appearance of the material.

- If Restrata™ Wound Matrix is completely intact (no resorption has occurred) and the wound is clean and clear of infection, then leave the matrix in place and cover with primary and secondary dressings.
- If any of the Restrata™ Wound Matrix material has resorbed than remove the remaining material and replace with a new piece of Restrata™ Wound Matrix (refer to section 6).
- Administer the VAS Foot and Ankle questionnaire.

6) REAPPLICATION OF RESTRATA™ WOUND MATRIX:

- Restrata™ Wound Matrix needs to be reapplied weekly over previously absorbed material (see section 3) steps 2 & 3).
  - However, if Restrata™ Wound Matrix is completely intact, no material, resorption has occurred and the wound is clean and clear of infection than the matrix does not have to be reapplied.
- In the event the material does need to be removed from the wound bed prior to reapplication, use warm (37°C) sterile saline to continuously rinse the wound site to help detach the material, so as not to cause further damage to the wound bed. Forced removal may result in wound reinjury.

  NOTE: If excess exudate collects under Restrata™, the material should be thoroughly fenestrated to allow the exudate to drain.

5.3. Post-Application Procedures

- Patients should be instructed on how to care for the surgical site, utilize the CAM walker, and keep the surgical site moist, and clean.
- Patients are required to return to the clinic every week for post-operative analysis of the wound site.

5.4. Follow-Up Procedures (Weekly up to 12 weeks or until complete closure is first identified with a confirmation visit within 2 weeks thereafter; window for all visits is ± 3 days)

At each of the interim timepoints subjects will return to the clinic for analysis / assessment of the following as indicated in the Schedule of Events in Appendix A:

- Measurement of wound area via acetate tracing
- Documentation of wound appearance via photograph
- Documentation of wound closure (if present)
- Gross observation of wound for evidence of infection

- Assessment of Quality of Life- Odor (only at 4, 8, 12 weeks ± 3 days)
- Assessment of Quality of Life- Itch (only at 4, 8, 12 weeks ± 3 days)
- Assessment of Quality of Life- Visual appearance
- Codes used to submit for reimbursement and amount (if any) reimbursed

5.5. Adverse Event Assessments

Assessment of safety is documented on the Adverse Events forms. The investigator should document any reported adverse events that occur outside of interval visits. Documentation of Adverse Events should include type, severity and relatedness to the device.

5.6. Early Withdrawal

Patients who withdraw prior to the 12 week endpoint who have not yet been confirmed to have completely closed at the confirmation visit will be contacted by phone and/or mail. The purpose of making contact will be to determine the status of the wound to the best of the patient's ability (i.e., healed, not healed, seeking additional treatment, not seeking additional treatment) and to complete as many of the patient-reported outcomes questionnaires as possible. Information obtained on these withdrawn patients will be counted toward the actual follow-up rate, but used only for the analysis of tertiary endpoints.

6. ASSESSMENT VARIABLES

6.1. Demographics

Demographics, including presenting symptoms, primary diagnosis, concomitant medical problems, and treatment history, will be collected from the information recorded at the Pre-Application interval.

6.2. Wound Assessment

Wounds will be assessed through gross observation and analysis for signs of infection, wound progression, and tissue healing. Gross observation will be utilized

to determine the necessity of graft reapplication or standard dressing change. Wound area measurements will be conducted via acetate tracings.

6.3. Safety

See section 8 for safety assessment information.

7. ADVERSE EVENT (AE)

7.1. Principal Investigator Responsibilities

The Principal Investigator (PI) and/or staff participating in the study shall document all adverse events as defined in section 7.3 of this protocol. The severity of the AE and its relationship to the procedure / device will also be assessed by the PI. The PI will document on the CRF any relatedness descriptions that might apply to the AE (e.g. none, possible, probable, and definite). The sponsor will designate a monitor to review patient medical records at the study locations for indications of adverse events throughout the study to ensure appropriate documentation and reporting.

Reimbursement data collected in the study requires purchase of the Restrata™ material so that the investigator is able to submit for reimbursement from payers. The purchase price will be agreed upon within the Clinical Trial Agreement.

7.2. Preexisting Conditions

In this study, a preexisting condition (i.e., present before the adverse event reporting period started that are noted on the preop medical history form) should not be reported as an adverse event.

7.3. Adverse Event Definitions

7.3.1. Device Related Adverse Event (AE)

A device related adverse event is any undesirable untoward response to the medical device experienced by a patient during the course of the study.

7.3.2. Serious Adverse Event (SAE)

A serious adverse event is any undesirable adverse event or untoward medical occurrence (sign, symptom, illness, abnormal laboratory value, or other medical event) experienced by a patient during the course of the study that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Requires intervention to prevent a permanent impairment of a bodily function or damage to a body structure.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room for a bronchospasm or convulsions that do not result in hospitalization.

This definition of an SAE is not intended to include hospitalization specifically to treat a condition that existed prior to the patient's enrollment in the study (e.g., pre-existing cardiovascular disease that is treated during the study) or prearranged elective surgery performed during this study period.

7.4. Adverse Event Severity Determination

All Adverse Events must be classified by the investigator using mild, moderate, or severe to determine the level of severity of the AE as it relates to the evaluation of patient safety through the full course of the AE from initial reporting to the end of study for each patient who participates in this clinical study.

ADVERSE EVENT SEVERITY

Mild	AE is noticeable to the patient but does not interfere with routine activity and does not require medical treatment.
Moderate	AE interferes with routine activity but responds to symptomatic therapy or rest. Usually requires medical treatment.
Severe	AE that results in loss of life or limb.

7.5. Adverse Event Reporting

Investigators and /or study staff are required to report AEs per their Institutional Review Board Standard Operating Procedures (IRB-SOPs).

8. DATA ANALYSIS

8.1. Demographics and Outcomes

Descriptive statistics will be used to compare amongst experimental groups, along with confidence intervals where appropriate to measure effect size. Rates of adverse events will be tabulated by type, severity and device / procedure relatedness. Furthermore, statistics on the wound measurements over time and at the 12 week endpoint will be used to inform future study hypotheses.

9. DATA HANDLING AND RECORD KEEPING

9.1. Case Report Forms (CRFs)

Completed original CRFs are the sole property of Acera and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from Acera.

It is the Principal Investigator's responsibility to ensure completion of CRFs by the clinical research team and to review and approve the data captured on all CRFs as accurate. All CRFs must be signed by the investigator. This signature serves to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all data entered on CRFs. Subject source documents are the investigator's subject records maintained at the study site, and will be used to verify data documented on CRFs.

In some cases, a portion of the source documents for a given study/site may be the CRFs. For this study, the patient questionnaires' CRF pages will be considered source documents.

10. ETHICS

10.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to obtain prospective approval of the conduct of the clinical study, the final protocol, protocol amendments, informed consent forms, and other relevant documents (e.g. advertisements), if applicable, from the IRB/IEC. Copies of the final IRB/IEC approvals must be forwarded to Acera prior to enrolling patients or starting any clinical study activities.

Protocol amendments require Acera and IRB/IEC approval before any patient in this clinical study is subjected to that change. When a change is necessary to eliminate apparent immediate hazards to the clinical study patients, emergency procedures can be used with caution to prevent exposing the patient to the hazard.

10.2. Ethical Conduct of the Clinical Study

This clinical study will be conducted in accordance with the protocol, Good Clinical Practice (GCP) guidelines, and applicable local regulatory requirements and laws.

11. PATIENT INFORMATION AND INFORMED CONSENT

The informed consent form must be agreed to by Acera and the IRB/IEC and must be in compliance with GCP guidelines, local regulatory requirements, and legal requirements.

The investigator must ensure that each study patient, or his/her acceptable representative, is fully informed about the nature and objectives of the clinical study and possible risks associated with participation in this study. The investigator will obtain written informed consent from each patient or their acceptable representative before any study-specific activity is performed. The informed consent form used in this study, and any changes made during the course of the study, must be

prospectively approved by both the IRB/IEC and Acera before use. The investigator will retain a copy of each patient's signed consent form.

12. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, device safety concerns or at the discretion of Acera.

Acera reserves the right to discontinue the study prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating patients within 30 days.

13. SUMMARY OF PROTOCOL REVISIONS

Revision Number	Date	Sections Revised	Summary of Changes
01	10/12/17	1, 3, 5.2 (subsections 4, 5, 6), 5.4, 13, and 14	Updated protocol sections for change in re-application rate of Restrata™ Wound Matrix from 4-week to weekly intervals.

14. APPENDICES

Appendix A: Schedule of Events

Procedure	Run-In / Screening Period			Treatment Period Up to 14 Weeks													Closure Confirmation Visit
	First visit	End Week 1	End Week 2	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	
Informed consent	X																
Screening	X	X	X														
Demographics / medical history CRF	X																
Passed screening / enrollment CRF			X														
Device application CRF				X	X	X	X	X	X	X	X	X	X	X	X		
Wound assessment CRF and photo				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Odor, itch, appearance CRF				X				X				X				X	
Adverse event CRF				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reimbursement CRF				X	X	X	X	X	X	X	X	X	X	X	X		
Patient stipend					X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix B: Supplies Provided by Acera

- Clinical Report Forms (CRFs)
- Study binder
- Pregnancy tests
- Acetate tracing supplies
- Patient stipend cards
- Controlled ankle movement (CAM) walker boots