Assessment of Wound Closure Comparing Synthetic Hybrid-Scale Fiber Matrix with Standard of Care in Treating Diabetic Foot Ulcer

Protocol Number: 21-RES-002
Revision: 02
Approval Date: 07NOV2022

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PROTOCOL APPROVAL SIGNATURE PAGE

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Pamela McKeown Vice President, Health Policy and Reimbursement Acera Surgical, Inc.	Date
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with this protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements and laws.

I hereby confirm that I approve of this Clinical Study Protocol and agree to comply with its terms as laid out in this document. I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

_____

Printed Name Signature Date

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1. PROTOCOL SUMMARY

Title	Assessment of Wound Closure Comparing Synthetic Hybrid-Scale Fiber Matrix with Standard of Care in Treating Diabetic Foot Ulcer
Protocol Number	21-RES-002; Revision: 002
Protocol Approval Date	07NOV2022
Study Sponsor	Acera Surgical, Inc.
Indications for Use	Restrata® 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 wounds (e.g., donor site / grafts, postlaser surgery, post-Mohs surgery, podiatric wounds, dehisced wounds), trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), draining wounds.
Study Product	Synthetic Hybrid-Scale Fiber Matrix (Restrata®)
Study Purpose	Comparatively assess wound closure in diabetic foot ulcers treated with synthetic hybrid-scale fiber matrix or standard of care in a randomized clinical trial.
Enrollment Size	48 subjects (24 subjects in the experimental arm and 24 subjects in the control arm)
Study Design	Prospective, randomized, controlled, single-blind clinical trial
Primary Outcome Measure	• Diabetic Foot Ulcers: Complete re-epithelialization of wounds within 12 weeks after the initial application of the study product plus confirmation of no drainage or need for additional dressing 2 weeks after complete re-epithelialization
Secondary Outcome Measure	1. Decrease in wound area 2. Time from initial application of study product to complete re-epithelialization of wound 3. Total number of product applications
Tertiary Outcome Measure	1. Quality of Life - SF-36 Questionnaire 2. Incidence of adverse events 3. Cost effectiveness / economic model (amount of product usage, length of treatment)
Assessment Timepoints	➢ Run-In Period to verify enrollment criteria: 2 weeks before initial application of study product ➢ Product Application: Weekly application (or as needed based on the clinician discretion and ongoing wound assessment) for either 12 weeks or until complete reepithelialization (whichever occurs first)

	➢ Wound assessment, measurement, and AEs: Day of initial product application and weekly for either 12 weeks or until complete re-epithelialization (whichever occurs first) ➢ Quality of Life and Pain Assessments: Day of initial product application and at either complete reepithelialization or 12 weeks (whichever occurs first) ➢ For patients with complete re-epithelialization: o Clinic visit two weeks after complete re-epithelialization to verify wound closure, drainage, and need for additional dressing

2. INTRODUCTION & PURPOSE

2.1. Background and Purpose

Diabetes and peripheral vascular disease are both growing healthcare problems that can lead to chronic wounds by compromising skin integrity and impairing the wound healing process[1]. Chronic wounds affect more than 6.5 million patients annually in the United States[2]. In particular, many diabetic foot ulcers (DFUs) fail to heal with standard options such as debridement, dressings, and infection control[1]. Skin substitutes can regenerate tissue and replace lost skin for wounds that are otherwise difficult to treat[2].

The process of wound healing requires a coordinated effort of cellular recruitment and tissue growth. Regenerative matrix materials have been used as a skin substitute to promote this coordination and provide immediate wound coverage to minimize the risks associated with infection and fluid loss[3]. 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.

To support the infiltration of fibroblasts, the deposition of new collagen, and reepithelialization of the wound surface, the wound matrix material should persist in the wound for several 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.

There remains a need for materials that minimize inflammation and promote complete wound healing. 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[5].

In 2018, a retrospective study was completed to evaluate clinical efficacy and utility of Restrata, a synthetic skin substitute[2]. The study examined 82 chronic wounds including 34 DFUs, 34 VLUs, and 14 other chronic wounds (pressure ulcers, traumatic and postsurgical wounds, nonvenous vascular wounds and necrotic wounds). Synthetic hybrid-scale fiber matrix was applied weekly, or as deemed appropriate for up to 12 weeks. Overall, treated wounds demonstrated progressive and sustained wound area reduction over the course of treatment, with 85 percent achieving complete closure at 12 weeks.

Based on these clinical findings a prospective, non-randomized, single-arm, single-blind study was conducted at 5 centers across the United States as a pilot for an expanded randomized controlled trial. In the study wounds were prepared using standard methods or debridement, and synthetic hybrid-scale fiber matrix was then applied to the wound so that it completely contacted the entire surface of the wound bed. A non-adherent primary wound dressing was then applied, followed by appropriate secondary dressing to manage the wound exudate and moisture. Post-application, wounds were examined weekly for signs of infection, wound progression, and tissue healing for up to 12 weeks, or until complete closure, which was confirmed 2 weeks thereafter. The wound area was measured, wound appearance was photographed, and wound closure was documented if present. Synthetic hybrid-scale fiber matrix was then re-applied weekly or as deemed appropriate.

At the end of the 12-week treatment period, complete wound closure occurred in 75.0% (18/24) of patients who received synthetic hybrid-scale fiber matrix. The average wound area reduction over 12 weeks was 96%, and the average time to complete wound closure was 6.4 weeks. A significant increase in epithelialization was observed from the initial to the final assessment ($p<0.0001$, Wilcoxon matched-pairs signed rank test), with nearly complete covering seen at final assessment. This was paralleled by a significant decrease in the amount of wound exudate ($p<0.0001$) to a nearly dry wound at the final assessment, and complete disappearance of necrotic tissue over time ($p=0.0001$). An average of 4.3 scaffolds were used per patient over the treatment period. Fixation was used to hold all scaffolds in place, with the most popular fixation technique being the use of Steri-Strips. The decision of the frequency of re-application was solely at the discretion of the clinician who was treating the wounds, and results found that half of the patients received reapplication of the nanofiber matrix on a weekly basis, whereas the other half of the patients had less frequent re-application rates. Neither fixation technique nor application frequency were found to have a statistically significant effect on

complete wound closure (p=0.41, Chi-square test and p=0.64, Fisher's exact test, respectively). In total, the clinical results suggest that synthetic hybrid-scale fiber matrix offers a new and unique alternative in the treatment of chronic DFUs and assists in properly powering an expanded multi-center randomized controlled clinical trial.

2.2. Purpose

The purpose of the following prospective, randomized, controlled clinical trial is to compare synthetic hybrid-scale fiber matrix (Restrata®, Acera Surgical, Inc.) with standard of care in treating diabetic foot ulcers in human subjects.

This study is being conducted to provide information on healing success with a new category of synthetic skin substitutes recently created by the Centers for Medicare and Medicaid Services (CMS). The study will demonstrate utilization of synthetic hybrid-scale fiber matrix in generating wound healing outcomes; including time to wound epithelialization, decrease in wound size, and total number of study product applications prior to healing. This data is valuable to the payor community with coverage decisions.

2.3. Intended Use/Indications

Restrata® is a sterile, single use device intended for use in local management of wounds. Restrata® is a soft, white, conformable, non-friable, absorbable matrix that provides 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® is terminally sterilized, in a single use double peel package in a variety of sizes. Contents of the package are guaranteed sterile and non-pyrogenic unless the package has been opened or damaged.

Restrata® 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 wounds (e.g., donor site / grafts, postlaser surgery, post-Mohs surgery, podiatric wounds, dehisced wounds), trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), draining wounds. Utilization of Restrata® in the treatment of diabetic foot ulcers,

as proposed in the present study, is therefore considered "on label" and is not considered experimental.

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

2.4. Standard of Care

The standard of care for established chronic wounds incorporates common principles, including:

- Removing necrotic tissue through debridement.
- Maintaining moisture balance by selecting the proper wound dressing to control exudate.
- Taking measures to prevent or treat wound infections.
- Correcting ischemia in the wound area.
- Applying offloading device in the case of diabetic foot ulcers)

Subjects randomized to the Standard of Care (control) arm will have their wounds debrided weekly. An appropriate dressing (foam or alginate dressing) will then be applied to maintain wound moisture balance in the wound, and changed daily. An appropriate offloading device (CAM boots or surgical shoes) will also be utilized depending on the wound location, condition and patient's health status.

3. STUDY DESIGN

Condition: Diabetic Foot Ulcer (DFU)

Aim: Comparatively assess wound closure in diabetic foot ulcers treated with synthetic hybrid-scale fiber matrix or standard of care in a randomized, controlled clinical trial.

Number of Patients: 48 subjects (24 subjects in the experimental arm and 24 subjects in the control arm)

Number of Sites: 2

Study Type: Interventional

Study Design: Allocation: Randomized (1:1 ratio)
Endpoint Classification: Efficacy
Intervention Model: Direct assignment

Masking: Single Blind (Subject)
Primary Purpose: Treatment

Control Group: Treatment with Standard of Care (weekly)

Test Group: Treatment with Synthetic Hybrid-Scale Fiber Matrix (weekly or as needed based on the clinician discretion and ongoing wound assessment)

Primary Outcome Measures:

- Complete re-epithelialization of wound as assessed by the evaluator within 12 weeks after the initial application of the study product plus confirmation of no drainage or need for additional dressing 2 weeks after complete re-epithelialization.

Secondary Outcome Measures:

- Decrease in Wound Area From Initial Application

  Wound area measurements will be made via acetate tracing every week for 12 weeks or until complete reepithelialization, whichever occurs first.

- Time to Complete Re-epithelialization

  The number of weeks from initial application of study product until complete reepithelialization is first identified.

- Number of Product Applications

  The number of study product applications including the initial application until 12 weeks for DFU patients or until complete reepithelialization, whichever occurs first.

Tertiary Outcome Measures:

- Quality of Life (SF-36)

  Day of initial application and at either 12 weeks or at complete re-epithelialization (whichever occurs first).

- Incidence of adverse events

- Cost effectiveness / Economic model (amount of product usage, length of treatment)

  The following information will be provided for each subject:

  - CPT Codes
  - HCPCS Codes
  - ICD-10 codes
  - DRGs (if applicable)
  - Dates of Service/Range of service
  - Place of Service
  - Bill type (131, etc.)

4. PATIENT SELECTION

4.1. Inclusion Criteria

1. Patient is at least 18 years old
2. Patient is willing and capable of complying with all protocol requirements
3. Patient or legally authorized representative (LAR) is willing to provide written informed consent prior to or at the beginning of the run-in period
4. Patient has Type 1 or Type 2 diabetes (criteria for the diagnosis of diabetes mellitus per American Diabetes Association)
5. Ulcer must be located at least in part on the foot or ankle
6. Ulcer must be present for a minimum of 28 days prior to randomization and initial application of study product
7. Wound size must be $\leq$30 cm^2 on the day of randomization and initial application of the study product, after initial debridement
8. Patient has adequate circulation to the affected extremity, as demonstrated by at least ONE of the following within 60 days prior to enrollment/randomization:

   a. Dorsum transcutaneous oxygen test (TcPO2) of study leg with results ≥40mmHg, OR

   b. Ankle-Brachial Index (ABI) of study leg with results of ≥ 0.7OR

c. Toe-Brachial Index (TBI) of study extremity with results of > 50 mmHg

4.2. Exclusion Criteria

1. Patient has been previously enrolled into this study, or is currently participating in another drug or device study that has not reached its primary endpoint
2. Patient is pregnant, breast feeding or planning to become pregnant
3. Patient has a known allergy to resorbable suture materials, e.g. Polyglactin 910 (PGLA), Polydioxanone (PDS)
4. Patient has a life expectancy less than six months as assessed by the investigator
5. Patient has received skin substitutes during the run-in period or within 14 days prior to beginning of run-in period
6. Patient has an additional wound within 3 cm of the study wound
7. Hgb A1c > 12% within 3 months prior to randomization in patients with a known history of diabetes
8. Patient not in reasonable metabolic control in the judgment of the investigator
9. Patient with a known history of poor compliance with medical treatments
10. Patient currently undergoing cancer treatment
11. Patient has been diagnosed with at least one of the following autoimmune connective tissue diseases: lupus, vasculitis, sickle cell, or uncontrolled rheumatoid arthritis
12. Patient is taking parenteral corticosteroids or any cytotoxic agents for 7 consecutive days during the run-in period or up to 30 days before the run-in period. Chronic oral steroid use is not excluded if dose is < 10 mg per day for prednisone.
13. Active infection, undrained abscess, or critical colonization of the wound with bacteria in the judgment of the investigator
14. Osteomyelitis or exposed bone, probes to bone or joint capsule on investigator's exam or radiographic evidence
15. Patient unwilling to or unable to safely utilize appropriate offloading device to unweight wound

16. Study ulcer experiences spontaneous closure over the 2-week run in period

5. STUDY CONDUCT

5.1. Schedule of Events

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

5.2. Screening

A patient screening log will be maintained. For patients who do not meet eligibility criteria, the reason(s) for exclusion from the study will be documented.

Patients will undergo the benefit insurance verification process via the third-party Reimbursement Support Hotline prior to or during the run-in period. Product Reimbursement will be confirmed for the synthetic hybrid-scale fiber matrix and related services and procedures incurred during the study period.

5.3. Informed consent

Prior to the start of the 2-week run-in period and the completion of any non-standard of care study activities, written informed consent shall be obtained from the patient or the patient's legally authorized representative (LAR). The investigator (or designee) must ensure that each patient (or LAR) is fully informed about the nature of the study, study objectives, study products, study procedures, and possible risks and benefits associated with participation in this study. Information shall be provided to the patient (or LAR) in a language and level of complexity so that he/she understands. The patient (or LAR) will have adequate time to consider participation in the study and have the opportunity to ask questions. The patient (or LAR) will sign and date the informed consent form, and he/she shall be provided a signed copy of the form. The investigator (or designee) will retain each patient's original signed informed consent form.

If significant new information is obtained after a patient is enrolled, the patient will be informed about the new information if the patient has not exited the study. Any discussions with the patient about new information should be documented. Patients will sign a new informed consent form at the discretion of the investigator and/or the IRB/EC.

The initial informed consent form and any revisions made during the course of the study must be approved by both the IRB/EC and Acera Surgical, Inc. before use.

5.4. Run-in Period

A 2-week run-in period will be required prior to enrollment/randomization and treatment in order to complete screening assessments and confirm that the wound has spontaneously closed. Written informed consent must be obtained prior to or at the beginning of the run-in period.

5.4.1. **First Visit of Run-In Period (14 to 17 days before randomization)**

An in-person visit will be completed at the beginning of the 2-week run-in period, and the following will be completed:

- Written informed consent will be obtained
- Assessment of inclusion/exclusion criteria
- Collection of demographics and medical history information
- Assessment of HbA1c in patients with known history of diabetes if it was not completed within the previous 73 days
- If vascularization in the study leg was not assessed within the previous 42 days, then at least ONE of the following shall be completed:
    - Ankle-brachial index (ABI) of study leg
    - Toe-brachial index (TBI) of study extremity
    - TcPO2 of study leg
- Assessment of ulcer size
- Assessment of wound for signs of infection, wound progression, and tissue healing. Gross observation will be utilized to determine the need for change in dressing type or dressing replacement/change.

NOTE: Informed consent must be obtained prior to the above assessments if they are not considered standard of care at this visit.

If the patient does not continue to meet all inclusion/exclusion criteria by the end of the visit, then they will be considered a screen failure and should not proceed with additional visits/assessments.

5.4.2. Second Visit of Run-In Period (7 days ± 3 days After First Visit)

An in-person visit will be completed 7 days after the first run-in visit (± 3 days), and the following will be completed:

- Assessment of ulcer size
- Assessment of wound through gross observation and analysis for signs of infection, wound progression, and tissue healing. Gross observation will be utilized to determine the necessity of standard dressing change.
- Continued assessment of inclusion/exclusion criteria.

  If the patient does not continue to meet all inclusion/exclusion criteria, then they will be considered a screen failure and should not proceed with additional visits/assessments.

5.5. Point of Enrollment

Patients will be considered enrolled after ALL of the following requirements are met:

- Written informed consent is provided
- The patient meets all inclusion criteria
- The patient meets no exclusion criteria
- The patient has completed the 2-week run-in period without spontaneous closure
- The patient is randomized

5.6. Randomization

The randomization process will be finalized prior to enrollment of the first study patient. Once the patient meets all enrollment criteria and has completed the 2-week run-in period, the patient will be randomized. Patients will be randomized to receive either synthetic hybrid-scale fiber matrix (treatment group) or standard of care treatment (control group). Appendix B presents the randomization plan.

Randomization will be stratified by wound size:

Patients will fall into two groups (< 12.5 cm^2) and (≥ 12.5 cm^2 and ≤ 30 cm^2). Patients within each group will be randomized in a 1:1 ratio to receive either synthetic hybrid-scale fiber matrix or standard of care treatment.

Once the patient is ready to be randomized, the randomization form will be completed by study personnel. Any patients that exit the study before randomization

are considered screen failures. A study exit CRF shall be completed if the patient is not eligible for randomization.

5.7. Blinding

The patient will remain blinded to the randomization assignment from the time of randomization assignment to the end of the treatment

5.8. 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 initial treatment with either Restrata or Standard of Care therapy.

5.9. Device Application / Follow-up Care Procedures

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

1) WOUND BED PREPARATION:

- 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 is necessary to ensure the wound edges contain viable tissue.

- Wait for any bleeding to stop and ensure there is no active bleeding before applying synthetic hybrid-scale fiber matrix.

- Cleanse the wound thoroughly with sterile saline prior to application of synthetic hybrid-scale fiber matrix

2) PREPARATION OF SYNTHETIC HYBRID-SCALE FIBER MATRIX

- Select the appropriate size sheet of synthetic hybrid-scale fiber matrix.
- ***Heavily fenestrate with a scalpel or mesh prior to application.*** Synthetic hybrid-scale fiber matrix must be fenestrated prior to use

in any wound prone to exudate in order to permit effective exudate management.

- Synthetic hybrid-scale fiber matrix 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.
- Synthetic hybrid-scale fiber matrix can be cut to the desired shape in a wet or dry state. In order to increase pliability of the product, hydrate in warm, sterile, hypertonic solution (i.e. saline, water, etc.) for a minimum of 1 minute.

3) APPLICATION OF SYNTHETIC HYBRID-SCALE FIBER MATRIX

- Apply matrix 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. The matrix can be repositioned as necessary.

- Securely anchor the matrix as needed with suture, staples or Steristrips.

- Apply a non-adherent primary wound dressing over the matrix.

- To prevent dislodgment of product, 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 matrix moist, and keep all layers securely in place. The optimum secondary dressing is determined by wound location, size, depth and provider preference.

- Discard any unused pieces of study product BEFORE the curtain between the patient's head and lower extremities is opened.

- Provide appropriate offloading device as appropriate based on the subject's wound location, health status etc.

5.10. Standard of Care

1) WOUND BED PREPARATION:

- 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 is necessary to ensure the wound edges contain viable tissue.

- Wait for any bleeding to stop and ensure there is no active bleeding before applying an appropriate primary dressing.

- Cleanse the wound thoroughly with sterile saline prior to application of an appropriate primary dressing.

2) APPLICATION OF PRIMARY / SECONDARY DRESSINGS

- Apply primary dressing to the wound bed, and position to completely contact the entire surface of the wound bed and extend slightly beyond wound margins.

- Securely anchor the dressing as needed.

- Apply appropriate secondary dressing to maintain dressing adherence, manage the wound exudate, and keep all layers securely in place. The optimum secondary dressing is determined by wound location, size, depth and provider preference.

- Discard any unused pieces of standard wound therapy BEFORE the curtain between the patient's head and lower extremities is opened.

- Provide appropriate offloading device as appropriate based on the subject's wound location, health status etc.

5.11. Post-Application Procedures

- Patients should be instructed on how to care for the wound site, utilize an appropriate offloading device (CAM boots or surgical shoes), and keep the wound site moist, and clean.

- Patients are required to return to the clinic every week for post-operative analysis of the wound site.

5.12. 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
- 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
- Codes used to submit for reimbursement and amount (if any) reimbursed

5.13. Study Exits

5.13.1. **Study Participation Exit Points**

A patient's participation in the study will end after any of the following:

- Patients with complete re-epithelialization and closure confirmation
- Patients without complete re-epithelialization at 12 weeks
- Patient withdrawal
- Patient lost to follow-up
- Amputation of all or part of the study limb
- Closure of study
- Patient death

5.13.2. **Patient Withdrawal**

A patient (or patient's LAR) may choose to withdraw from the study at any time without penalty or loss of benefits. The patient should notify the investigator (or designee) of his/her desire to withdraw, and the investigator (or designee) should ask for and document the reason for withdrawal. The investigator may also choose to withdraw a patient from the study at any time if he/she considers it to be in the patient's best interest. The reason for withdrawal should be recorded. Any data collected on the patient up to the point of withdrawal may be used in the study.

If complete wound closure has not been confirmed at the time of withdrawal from the study, then the investigator should attempt to

determine the status of the wound at the time of the patient's withdrawal 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 the patient is able and willing to complete.

5.13.3. **Patient Lost To Follow-Up**

The investigator should encourage patients to return for all required follow-up visits. A patient will be considered lost to follow-up after three documented phone call attempts or emails plus a certified letter that is sent to the patient's last known address in which no response is received. A patient should not be automatically exited from the study after a missed visit(s). Rather, the patient will remain in the study until he/she completes the final study visit required by the protocol, withdraws from the study, or is considered to be lost to follow-up.

5.13.4. **Patient Death**

If known, the cause of death should be documented.

5.13.5. **Sponsor Discontinues Study**

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

6. ADVERSE EVENT

6.1. Principal Investigator Responsibilities

The investigator (or designee) should record and maintain all adverse events that occur over the course of the patient's participation in the study (randomization through study exit) during or outside of study visits. Adverse events that are reported to the sponsor will be assessed by an investigator. Adverse event assessments should include severity, seriousness, and relatedness to the product, study procedures and pre-existing conditions. See Section 6.4 for adverse events that are required to be reported to the Sponsor.

6.2. Adverse Event Definitions

Adverse Event:

Any untoward medical occurrence (sign, symptom, illness, abnormal laboratory value, or other medical event) that occurs while the patient is enrolled in the study whether or not it is related to the study product or study procedures. A medical condition (pre-existing condition) that exists at study enrollment/randomization is not considered an AE unless the condition worsens after enrollment.

Serious Adverse Event:

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 study that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability/incapacity; or
- 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 a serious adverse 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 adverse 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.

Adverse Device Effect:

Any adverse event that is caused by or associated with a study product.

Unanticipated Adverse Device Effect:

Any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a study product, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the Protocol or Instructions for Use.

6.3. Adverse Event Assessment

Adverse events that are required to be reported to the sponsor must be assessed by an investigator for severity, seriousness and relatedness to the product, study procedures and pre-existing conditions.

The following scale should be used for severity assessment:

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 and/or requires medical treatment
Severe	AE results in loss of life, loss of limb, is life threatening, or results in permanent impairment of body structure or function

The following scale should be used for an assessment of relatedness to the study product, study procedure(s), and pre-existing conditions:

- Not Related
- Possibly Related
- Probably Related
- Definitely Related

6.4. Adverse Event Reporting

The following adverse events are required to be promptly reported to the sponsor on the adverse event CRF:

- Any serious adverse event whether or not it is related to a study product/procedure

- Any adverse event that in the opinion of the investigator is definitely related, probably related, or possibly related to a study product and/or study procedure

- The following adverse events whether or not they are related to a study product/procedure:

    o Infection of wound and/or area surrounding wound

    o Complete or partial amputation of lower extremity

    o Allergic reaction

Serious adverse product effects should be reported to the sponsor as soon as possible. Pre-existing conditions or adverse events that occur prior to randomization are not required to be reported.

The investigator (or designee) is also required to report AEs to the IRB/EC if the AEs are required to be reported per the IRB/EC reporting requirements.

7. STATISTICAL CONSIDERATION

7.1. Hypotheses to be Tested

7.1.1. **Primary Endpoints:**

The null hypothesis (H_0) for the primary endpoint is that the difference in proportion of patients achieving 100% re-epithelialization by week 12 between the synthetic hybrid-scale fiber matrix group (π_1) and the control group (π_2) is less than or equal to the superiority margin of +0.10 based on a one-sided Farrington & Manning test. The alternative hypothesis (H_1) is that the difference is less than the superiority margin of +0.10. These can be seen in the equations below:

$$H_0: \pi_1 - \pi_2 >= +0.10$$
$$H_1: \pi_1 - \pi_2 < +0.10$$

7.2. Analysis Populations

Intention to Treat Population (ITT)
The ITT population will consist of all enrolled patients. Patients are considered enrolled after meeting the criteria specified in Section 4. Patients in the ITT

population will be evaluated based on the randomized treatment group.

Modified Intention to Treat Population (mITT)
The mITT population will consist of ITT patients who have at least one product application. This will serve as the primary analysis population for study efficacy. Patients in the mITT population will be evaluated based on the randomized treatment group.

Per Protocol (PP)
The PP will include all ITT patients who additionally meet all study eligibility criteria, have available study data for the primary study endpoint and do not have a major protocol violation that affects primary effectiveness. Patients in the PP population will be evaluated based upon the treatment that they receive.

7.3. Sample Size Calculation

Sample size calculations were performed using a Farrington & Manning test for superiority of the synthetic hybrid-scale fiber matrix group compared to the control group. Under assumptions of a closure rate of 80% for the synthetic hybrid-scale fiber matrix group, 40% for the control group, and a superiority margin of 10%, this results in a sample size of 20 per group (40 total) that provides a power of 0.8 and one-sided alpha of 0.05. After allowing for an assumed 20% lost to follow up, this results in a total sample size of 48 patients.

7.4. Interim and Final Analyses

An unblinded interim assessment for sample size re-estimation (SSR) will be performed on the primary endpoint of the study by an independent statistician. The analysis will be conducted when 50% of the mITT population (24 patients) have been enrolled and completed the primary endpoint evaluation. The analysis described below will be performed on the mITT population.
The purposes of the interim analysis are (1) to calculate the power for superiority, conditioned on the interim-observed difference between treatments with respect to 100% re-epithelialization rates and on the superiority margin of 10%, and (2) determine if the sample size needs to be increased in order to maintain the desired conditional power of 80%.

The conditional power will be calculated under the assumption that the interim observed estimate of the treatment difference is the true treatment difference. It will be calculated using the following formula as discussed in Lan and Wittes (1988) where:

$$1 - \Phi[\frac{Z_{1-\alpha} - B_{\tau} / \tau}{\sqrt{1-\tau}}]$$

$Z_{1-\alpha}$ is the (1-α)*100% percentile of the standard normal distribution (i.e., the critical value used to assess superiority at the final analysis at overall one-sided significance level α).
τ is the information fraction (= proportion of patients in the first interim analysis = r/M where r is the number of patients per group in the interim analysis and M is the planned number of patients per group for the final analysis); if the interim sample sizes per group are not equal due to randomness, the harmonic mean of the sample size will be used.

$B\tau = Z_{\tau}\sqrt{\tau}$ where Zτ = the Farrington-Manning non-inferiority test statistic calculated on the interim observed data. Φ is the cumulative distribution function of the standard normal distribution.
Following the "promising zone" algorithm in Mehta and Pocock (2011), if the conditional power based on the planned final sample size of 48 patients is <42% or >80% at the interim stage, the study will continue as is (there will be no stoppage of the study for futility nor will there be a sample size increase). If the conditional power is between 42-80% (the promising zone), the sample size may then be re-estimated using the method described by Wang et al (2002) in order to maintain 80% conditional power without increasing the Type I error (probability of a false positive result) of the study. Specifically, the total revised sample size per group, M` required to achieve a conditional power of 80% to assess superiority at the final analysis using a superiority margin of 10% is found by solving the following equation for M`:

$$Z_{0.20}\sqrt{1 - \frac{r}{M`}} + Z_{\tau}\sqrt{\frac{M`}{r}} - Z_{1-\alpha} = 0$$

where $Z_{0.20}$ is the 20th percentile of the standard normal distribution (corresponding to the desired 80% conditional power) and where all other variables in this equation are defined above. M` will not exceed 70 patients for the DFU arm. This formula assumes the interim observed effect size between treatments is the true effect size between treatments.

Results of the interim assessment will be presented by the independent statistician to the Sponsor group. The report to the Sponsor will state if additional sample is required to achieve a conditional power of 80%, and if so, how many additional patients. If additional sample size is required, the Sponsor will make a decision to either enroll the additional patients or not enroll and accept that the primary

endpoint may be under-powered. The independent statistician's report containing the results that led to the independent statistician's recommendation will be kept confidential within the select Sponsor group.

The following decision rules outline the possible outcomes of the interim analysis:

1. If the test for CPni <0.42 or ≥0.8, then there is no increase in the sample size and the trial will be completed on a minimum of 48 enrolled patients, as scheduled.
   If the test for conditional power is $0.42 \leq CPni < 0.8$, then the sample size will be increased by just the right amount such that CPni is increased to 0.8, under a cap of 70 patients. The range $0.42 \leq CPni < 0.8$ is called the promising zone for non-inferiority. Specifically, if CPni is in its promising zone, this decision rule increases the sample size by the smallest of 70 patients or the number needed to boost CPni to 0.8.

7.5. Statistical Analysis

Data collected in this study will be reported using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics (number of patients, mean, standard deviation [SD], median, minimum, and maximum). Categorical variables will be summarized using frequencies and percentages of patients in each category. All results will be presented by treatment group and study arm in appropriate patient populations. SAS software version 9.4 or similar will be used for the statistical analysis.

7.5.1. **Demographic and Baseline Characteristics**

Patient demographics for all analysis populations will be summarized in a table. Gender, ethnicity, and race will be summarized with frequency and percent. Age, height, weight, and BMI will be summarized with N, mean, standard deviation, median and minimum and maximum.

7.5.2. **Medical History**

Patient medical history, including tobacco use, comorbidities, diabetes history, and wound history (where applicable) for all analysis populations will be summarized in a table. Categorical variables will be summarized with frequency and percent. Continuous variables will be summarized with N, mean, standard deviation, median and minimum and maximum.

7.5.3. **Procedural Information**

Descriptive statistics will be used to summarize the initial wound assessment by treatment group and procedural information.

7.5.4. **Primary Endpoints**

For the purpose of the primary endpoint analysis, the largest study wound will be analyzed.

7.6. Study Outcome

7.6.1. **Primary Endpoints**

100% re-epithelialization will be assessed every week for 12 weeks or until 100% re-epithelialization, whichever occurs first. Persistence of wound closure will be verified via confirmatory visit within 2 weeks after complete closure has been first determined.
For the primary endpoint of 100% re-epithelialization at week 12 a two-stage analysis will test first if the rate of 100% re-epithelialization is superior between groups using a chi squared and/or Farrington & Manning test. Superiority for synthetic hybrid-scale fiber matrix will be demonstrated if the lower bound of the 90% CI of the difference in proportions lies above the superiority margin of +10%.

7.6.2. **Secondary Endpoints**

The following secondary endpoints will be summarized for exploratory purposes. Statistical testing may be performed at the request of the sponsor / investigator.
Decrease in Wound Area from Baseline
The difference in wound area from baseline to each time point will be summarized for each treatment group in each arm. The difference in mean percent change in size between the treatment group and control group will be calculated for each timepoint. Wound area measurements will be made via acetate tracing every week for 12 weeks, or until 100% re-epithelialization, whichever occurs first.

Time to Wound Closure
The time to wound closure will be summarized by proportion of patients with wound closure at each timepoint for each treatment group in each arm. The difference in proportion of patients with wound closure between the treatment group and control group will be calculated for each timepoint.

Persistence of wound closure will be verified via confirmatory visit within 2 weeks after complete closure has been first determined.

Number of Product Applications

The number of product applications will be summarized for each treatment group in each arm. The difference in mean number of applications between the treatment group and control group will be calculated for each timepoint. Product applications will be defined as the number of product applications prior to complete wound closure within the treatment period for each study arm.

7.6.3. **Tertiary Endpoints**

The following tertiary endpoints will be summarized for exploratory purposes. Continuous variables will be summarized using descriptive statistics (number of patients, mean, median, quartiles, standard deviation [SD], minimum, and maximum). Categorical variables will be summarized using frequencies and percentages of patients in each category. Statistical testing may be performed at the request of the sponsor / investigator. Where possible, results will be summarized at each collected time point and the change from baseline will be presented.

Quality of Life – SF-36

Results will be summarized at each time point using the proportion of patients at each level. Change from baseline will be assessed as the number of levels either improved or worsened.

Cost effectiveness / Economic model (Amount of product usage, length of treatment)

Results will be summarized descriptively by timepoint where applicable.

7.7. Adverse Events

7.7.1. **All Adverse Events**

Summaries of incidence rates of individual AEs overall will be prepared. Only treatment emergent AEs will be analyzed (a treatment emergent adverse event is one that started or worsened in severity at or after start of randomized treatment). Because a patient may experience more than one AE, summaries will provide both the number of patients experiencing at least one event and the number of events within a reporting period. Percentages provided will be the percent of patients experiencing one or more adverse events. In addition, incidence of AEs will be presented by severity (mild,

moderate, severe) and by relationship to investigational product or procedure. Patients experiencing an event more than once will be counted under the maximum severity/relationship experienced.
A listing of all adverse events will include the patient number, AE number, days since index procedure, the AE name, the severity of AE, whether or not the AE is classified as serious (SAE), the relationship of the AE to the study product or procedure, the action taken, and the outcome.

7.7.2. **Serious Adverse Events**

Summaries of incidence rates and relationship to the study product/procedure of individual SAEs will be prepared. Summaries will provide both the number of patients and the number of events within a reporting period. Percentages provided will be the percent of patients experiencing one or more serious adverse events. A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF.

7.7.3. **Adverse Events of Interest**

Summaries of incidence rates of the following AEs by treatment group will be prepared:

- Infection of wound and/or area surrounding wound
- Amputation of lower extremity
- Allergic reaction
- Excessive redness, pain, swelling or blistering of wound

7.8. Strategies to Address Missing Data

Patients who are missing complete wound closure will be considered as “missing data patients”. Missing complete wound closure status will be imputed using a logistic regression multiple imputation approach for dichotomous outcome data. In this approach, missing healing status will be imputed from logistic regression models with independent variables of age, gender, and other variables to be specified in the formal statistical analysis plan. This will be performed 50 times in each arm in order to generate 50 “complete” datasets. The one-sided Farrington & Manning test for assessing treatment difference will be carried out on each of the 50 complete datasets, with the results being combined across the 50 complete datasets using standard multiple imputation theory to obtain one overall p-value

comparing the two treatments on the primary endpoint after accounting for missing data.

8. DATA HANDLING AND RECORD KEEPING

8.1. 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.

Maintenance of Records:
The Principal Investigator shall maintain the required records for a period of 2 years after the date the study is completed or terminated or the records are no longer required to support a submission to a regulatory agency, whichever date is later. The Principal Investigator may withdraw from the responsibility to maintain records for the time required by transferring custody to another person who will accept responsibility for them. The sponsor must be notified in writing about the records transfer.

9. ETHICS

9.1. Ethical Conduct of the Clinical Study

This clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, Good Clinical Practice (GCP) guidelines, and applicable local regulatory requirements and laws.

9.2. Institutional Review Board (IRB)

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. Copies of the final IRB approvals must be forwarded to Acera Surgical, Inc. prior to enrolling patients or starting any clinical study activities.

Protocol amendments require Acera Surgical, Inc. and IRB 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.

9.3. Confidentiality

Information about study patients will be kept confidential and managed according to the requirements of the local regulatory authority, as well as applicable US laws and regulations. Personal Health Information (PHI) will be acquired during informed consent of the patient and from the medical records. This information will be utilized to identify the subject and contact the subject for emergencies and follow up appointments. The PHI is part of the patient clinic chart, and will be secured in a locked office when not in use. To ensure that confidentiality is maintained, patient names will not be used in this evaluation in any other way. A unique identifying number will be used. This identification method will be consistent for each subject throughout the evaluation.

In the event that a patient revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of the authorization.

10. SPONSOR DISCONTINUATION CRITERIA

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. If the investigator suspends or terminates the study at their respective site, the investigator will promptly inform the Sponsor and the IRB/EC and provide them with a detailed written explanation.

10.1. Termination of the study by the Sponsor

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

Acera Surgical, Inc., 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.

10.2. Termination of Site by the Sponsor

Acera Surgical, Inc., reserves the option to terminate the participation of a study site at any time. Reasons for terminating the participation of a study site include, but are not limited to, the following:

- Patient enrollment is unsatisfactory
- Data recording is consistently inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study
- IRB decides to terminate or suspend approval for the Investigator
- Study site or Investigator violates GCP or the study agreements, disrupting the appropriate conduct of the trial.
- Investigator asks to withdraw from study participation

10.3. Termination by the Investigator

If the Investigator terminates the study prematurely, the Investigator must provide the Sponsor and IRB/EC with a written statement describing why the study was terminated prematurely.

11. PUBLICATIONS POLICY

Acera Surgical, Inc. will be responsible for determining when the study results should be published. The Sponsor may work jointly with the investigators to publish information. The investigators shall not submit a publication to journals or professional societies without notification and review by the Sponsor.

12. SUMMARY OF PROTOCOL REVISIONS

Revision Number	Date	Sections Revised	Summary of Changes
01	xx/xx/21		
02	21OCT2022	4.1 inclusion #7; 4.1 inclusion #8b; 4.2 exclusion #16 5.4 5.4.1 5.4.2 5.5 5.6 5.12 7.6.1 Appendix B	Including wounds ≤30cm2, remove lower limit on wound size, remove upper ABI limit, run-in period revised to remove wound size changes limitations, remove acetate tracing requirements, data analysis will be conducted using chi squared

13. REFERENCES

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2. Regulski MJ and MacEwan MR. Implantable Nanomedical Scaffold Facilitates Healing of Chronic Lower Extremity Wounds. Wounds. 2018;30(8): E77-E80.

3. Snyder DL, Sullivan N, Margolis DJ, Schoelles K. Skin substitutes for treating chronic wounds. Technology Assessment Program Project ID No. WNDT0818. (Prepared by the ECRI Institute-Penn Medicine Evidence-based Practice Center under Contract No. HHSA 290-2015-00005-I) Rockville, MD: Agency for Healthcare Research and Quality. February 2020.

4. Macewan M R, Macewan S, Kovacs T R, et al. (October 02, 2017) What Makes the Optimal Wound Healing Material? A Review of Current

Science and Introduction of a Synthetic Nanofabricated Wound Care Scaffold. Cureus 9(10): e1736. DOI 10.7759/cureus.1736

5. MacEwan MR and MacEwan S et al. Efficacy of a Nanofabricated Electrospun Wound Matrix in Treating Full-thickness Cutaneous Wounds in a Porcine Model. Wounds. 2018;30(2):E21–E24.

14. APPENDICES

Appendix A: Schedule of Events

Requirement	**Run-In Period**		**Treatment Period (1)** Week 0 is the initial application of study product and occurs 14 to 17 days after the start of the run-in period. Visit window for Weeks 1 through 12 is (±3 days)													**Two-Week In-person Follow-up (2)**
	Start	7 days (±3 days)	0	1	2	3	4	5	6	7	8	9	10	11	12	2 weeks after wound closure (±3 days)
Informed Consent	X															
Screening	X	X	X													
Demographic and history	X															
HbA1c	X(3)															
Vascularization (ABI, TBI or TcPO2)	X(3)															
Assessment of Re-Eoithelization				X	X	X	X	X	X	X	X	X	X	X	X	
SF-36 Questionnaire and Pain Scale			X												X(4)	
Randomization			X													
Visual Examination of Wound and imaging	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Product Application			X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X(2)

Notes:

- X – Requirement must be completed by study personnel
- (1) – Treatment period visits will cease after complete wound re-epithelialization is confirmed
- (2) – An in-person visit two weeks (± 3 days) after complete wound re-epithelialization is first identified after Week 0 are required for patients with complete wound re-epithelialization. These visits are NOT required if there is not complete wound re-epithelialization at or before 12 weeks.
- (3) – HbA1c and a vascularization assessment can be completed anytime within 60 days prior to Week 0
- (4) – SF-36 Questionnaire and Pain Scale will be completed during the visit when complete wound re-epithelialization is first identified or at 12 weeks (whichever occurs first)

Appendix B: Randomization Plan

A Randomization Plan for patients with wound size < 12.5 cm²

from

http://www.randomization.com

1. Standard of Care
2. Restrata
3. Restrata
4. Standard of Care
5. Restrata
6. Standard of Care
7. Restrata
8. Standard of Care
9. Restrata
10. Standard of Care
11. Restrata
12. Standard of Care
13. Standard of Care
14. Restrata
15. Restrata
16. Restrata
17. Restrata
18. Standard of Care
19. Standard of Care
20. Restrata
21. Standard of Care
22. Restrata
23. Standard of Care
24. Standard of Care

24 subjects randomized into 2 blocks
To reproduce this plan, use the seed 24156
along with the number of subjects per block/number of blocks
and (case-sensitive) treatment labels as entered originally.
Randomization plan created on 3/26/2021, 1:14:54 PM

A Randomization Plan for patients with wound size of ≥ 12.5 cm² and ≤ 30 cm²

from

http://www.randomization.com

1. Standard of Care
2. Restrata
3. Standard of Care
4. Restrata
5. Standard of Care
6. Restrata
7. Restrata
8. Standard of Care
9. Restrata
10. Restrata
11. Standard of Care
12. Standard of Care
13. Standard of Care
14. Restrata
15. Restrata
16. Standard of Care
17. Restrata
18. Restrata
19. Standard of Care
20. Restrata
21. Standard of Care
22. Standard of Care
23. Standard of Care
24. Restrata

24 subjects randomized into 2 blocks
To reproduce this plan, use the seed 27186
along with the number of subjects per block/number of blocks
and (case-sensitive) treatment labels as entered originally.
Randomization plan created on 3/26/2021, 1:17:57 PM

Appendix C: Supplies Provided by Sponsor

- Clinical Report Forms (CRFs)
- Study binder
- Acetate tracing supplies