Assessment of Wound Closure Comparing Synthetic Hybrid-Scale Fiber Matrix with Standard of Care in Treating Diabetic Foot Ulcers (DFU) and with Living Cellular Skin Substitute in Treating Venous Leg Ulcers (VLU)

Protocol Number: 21-RES-001

Revision: 03

Date: 30 September 2022

Acera Surgical, Inc.

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PROTOCOL APPROVAL SIGNATURE PAGE

Assessment of Wound Closure Comparing Synthetic Hybrid-Scale Fiber Matrix with Lyophilized Acellular Fish Skin in Treating Diabetic Foot Ulcers (DFU) and with Living Cellular Skin Substitute in Treating Venous Leg Ulcers (VLU)

Protocol Number: 21-RES-001

Revision: 01

2/8/2021

Matthew MacEwan, PhD — Date

Chief Science Officer

Acera Surgical, Inc.

2/8/2021

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Vice President, Health Policy and Reimbursement

Acera Surgical, Inc.

Feb 7, 2021

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Principal Investigator

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Assessment of Wound Closure Comparing Synthetic Hybrid-Scale Fiber Matrix with Standard of Care Standard of Care in Treating Diabetic Foot Ulcers (DFU) and with Living Cellular Skin Substitute in Treating Venous Leg Ulcers (VLU)

Protocol Number: 21-RES-001

Revision: 03

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 Ulcers (DFU) and with Living Cellular Skin Substitute in Treating Venous Leg Ulcers (VLU)

Protocol Number	21-RES-001; Revision: 03
Protocol Date	08 March 2021
Study Design	Prospective, randomized, single-blinded, comparison, non-inferiority study
Study Sponsor	Acera Surgical, Inc. 1650 Des Peres Rd., Ste. 120St. Louis, MO 63131 844-879-2237
Steering Committee	A Steering Committee consisting of physicians working with the Sponsor will provide guidance on study procedures, subject enrollment, adverse events and protocol compliance.
Study Product	Synthetic hybrid-scale fiber matrix (Restrata®)
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, post-laser surgery, post-Mohs surgery, podiatric wounds, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), and draining wounds.
Comparator Products	Standard of Care for patients with diabetic foot ulcers Living cellular skin substitute (Apligraf®) for patients with venous leg ulcers
Enrollment Size	• Diabetic Foot Ulcers: The initial planned enrollment is 110 patients. An interim analysis will be performed after 56 patients complete the primary endpoint. Based on the interim analysis result, the enrollment size may be increased to a maximum of 166 patients. • Venous Leg Ulcers: The initial planned enrollment is 60 patients. An interim analysis will be performed after 30 patients complete the primary endpoint. Based on the interim analysis result, the enrollment size may be increased to a maximum of 90 patients.
Primary Outcome Measure	• Diabetic Foot Ulcers: 100% re-epithelialization of wound within 12 weeks after the initial application of the study product plus confirmation of no drainage or need for additional dressing 2 weeks after 100% re-epithelialization

	• Venous Leg Ulcers: 100% re-epithelialization of wound within 16 weeks after the initial application of the study product plus confirmation of no drainage or need for additional dressing 2 weeks after 100% re-epithelialization
Secondary Outcome Measures	1. Decrease in wound area 2. Time from initial application of study product to 100% re-epithelialization of wound 3. Total number of product applications
Tertiary Outcome Measures	1. Quality of Life - SF-36 Questionnaire 2. Pain reported by patient 3. Incidence of adverse events 4. Ease of Use and handling of study product 5. Cost effectiveness / economic model (amount of product usage, length of treatment) 6. Reimbursement and/or payer access
Assessment Time-Points	➢ Run-In Period to verify enrollment criteria: 2 weeks before initial application of study product ➢ Product Application: o DFUs: ▪ Patients randomized to synthetic hybrid-scale fiber matrix: Biweekly application for either 12 weeks or until 100% re-epithelialization (whichever occurs first) ▪ Patients randomized to Standard of Care: Weekly dressing application for either 12 weeks or until 100% re-epithelialization (whichever occurs first) o VLUs: Biweekly application for either 16 weeks or until 100% re-epithelialization (whichever occurs first) ➢ Wound assessment, imaging, and AEs: o DFUs: Day of initial product application and weekly for either 12 weeks or until 100% re-epithelialization (whichever occurs first) o VLUs: Day of initial product application and weekly for either 16 weeks or until 100% re-epithelialization (whichever occurs first) ➢ Quality of Life and Pain Assessments: o DFU patients: Day of initial product application and at either 100% re-epithelialization or 12 weeks (whichever occurs first) o VLU patients: Day of initial product application and at either 100% re-epithelialization or 16 weeks (whichever occurs first)

	➢ For patients with 100% re-epithelialization: o Clinic visit two weeks after 100% re-epithelialization to verify wound closure, drainage, and need for additional dressing o Telephone call six-months after initial product application to verify wound closure, drainage, and need for additional dressing

2. INTRODUCTION & PURPOSE

2.1 Background

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) and venous leg ulcers (VLUs) 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.

Human autografts and allografts, animal-based xenografts, and fully synthetic materials have been used clinically with varying degrees of success.[4] 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.[3] 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%.

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.[5] 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.[6]

In 2018, a retrospective study was completed to evaluate clinical efficacy and utility of Restrata, a synthetic hybrid-scale fiber matrix.[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 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 patents received re-application 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 study is to compare synthetic hybrid-scale fiber matrix with standard of care in treating diabetic foot ulcers in human subjects, and to compare synthetic hybrid-scale fiber matrix with living cellular skin substitute in treating venous leg ulcers. Given the large number of skin substitute cellular tissue products in the marketplace, 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 with synthetic hybrid-scale fiber matrix and comparators 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 information is needed by the payor community in determining coverage and reimbursement for the new synthetic hybrid-scale fiber matrix.

2.3 Intended Use / Indications of the Study Product

Synthetic hybrid-scale fiber matrix (Restrata) received FDA 510(k) clearance effective April 26, 2017 (K170300). It is a sterile, single use product intended for use in local management of wounds. It 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. Synthetic hybrid-scale fiber matrix is a synthetic electrospun matrix that possesses a hybrid-scale fiber architecture similar to native extracellular matrix (ECM), indicated for use in the local management of wounds. The mechanism of action allows for cellular ingrowth and neovascularization before completely degrading via hydrolysis. Synthetic hybrid-scale fiber matrix is made from synthetic biocompatible materials. The product permits the ingress of cells and soft tissue formation in the defect space / wound bed. The product does not contain any human or animal materials or tissues.

Synthetic hybrid-scale fiber matrix is supplied terminally sterile, in a single use double peel package in a variety of sizes. It may be fenestrated or meshed with a scalpel 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. Contents of the package are guaranteed sterile and non-pyrogenic unless the package has been opened or damaged.

Synthetic hybrid-scale fiber 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. Synthetic hybrid-scale fiber matrix will be used for patients with a DFU(s) or VLU(s).

2.4 Intended Use / Indications of the Comparator Products

2.4.1: Standard of Care (SOC) will be used for patients with diabetic foot ulcers (DFUs)

Standard of Care will include preparation of the wound bed using sharp debridement to ensure it is free of exudate and devitalized tissue, an aseptic technique for application of a non-adherent primary dressing and an off-loading boot as applicable, as well as training on primary dressing changes (See Appendix B).

2.4.2: Living cellular skin substitute will be used for patients with venous leg ulcers (VLUs)

Living cellular skin substitute (Apligraf®), a commercially available product manufactured by Organogenesis, Inc., United States, is a skin substitute that looks, functions, and responds like healthy skin.[8] The epidermal layer contains living human keratinocytes and stem cells that provide potent healing signals (growth factors / cytokines). The dermal layer contains living human fibroblasts that are contained in a bovine Type I collagen lattice. Living cellular skin substitute is FDA-approved (PMA P950032) to treat venous leg ulcers and diabetic foot ulcers after four weeks and three weeks of failed conventional therapy, respectively. Living cellular skin substitute was chosen as a comparator as it is a skin substitute used frequently in the treatment of chronic venous leg ulcers.

3. STUDY DESIGN

Conditions : Diabetic Foot Ulcers (DFU) and Venous Leg Ulcers (VLU)

Aim: Assessment of complete wound re-epithelialization by comparing synthetic hybrid-scale fiber matrix with SOC in treating DFUs and with living cellular skin substitute in treating VLUs

Study Type: Interventional

Study Design: Prospective, randomized, single-blinded, comparison, non-inferiority study

Control Group: SOC for DFU patients and living cellular skin substitute for VLU patients

Test Group: Synthetic hybrid-scale fiber matrix for patients with DFUs and VLUs

Number of Sites: Up to 10

Number of Subjects:

- **Diabetic Foot Ulcers:** The initial planned enrollment is 110 patients, with no more than 27 DFU patients enrolled at each site. An interim analysis will be performed after 56 patients complete the primary endpoint. Based on the interim analysis result, the enrollment size may be increased to a maximum of 166 patients with a maximum of 41 DFU patients at each site.
- **Venous Leg Ulcers:** The initial planned enrollment is 60 patients, with no more than 15 VLU patients enrolled at each site. An interim analysis will be performed after 30 patients complete the primary endpoint. Based on the interim analysis result, the enrollment size may be increased to a maximum of 90 patients with a maximum of 22 VLU patients at each site.

Primary Outcome Measure:

- **Diabetic Foot Ulcers**:

  100% re-epithelialization of wound as assessed by the blinded evaluator via the eKARE inSight platform within 12 weeks after the initial application of the study product plus confirmation of no drainage or need for additional dressing 2 weeks after 100% re-epithelialization

- **Venous Leg Ulcers**:

  100% re-epithelialization of wound as assessed by the blinded evaluator via the eKARE inSight platform within 16 weeks after the initial application of the study product plus confirmation of no drainage or need for additional dressing 2 weeks after 100% re-epithelialization

Secondary Outcome Measures:

- Decrease in Wound Area from Initial Application

  Wound area measurements will be made via the eKare inSight platform every week for 12 weeks for DFU patients and 16 weeks for VLU patients, or until 100% re-epithelialization, whichever occurs first.

- Time to 100% re-epithelialization

  The number of weeks from initial application of study product until 100% re-epithelialization is first identified.

- Number of Product Applications

  The number of study product applications including the initial application until 12 weeks for DFU patients and 16 weeks for VLU patients, or until 100% re-epithelialization, whichever occurs first.

Tertiary Outcome Measures:

- Quality of Life (SF-36)
  - For DFU patients, day of initial application and at either 12 weeks or at 100% re-epithelialization (whichever occurs first)
  - For VLU patients, day of initial application and at either 16 weeks or at 100% re-epithelialization (whichever occurs first)
- Pain reported by patient
  - For DFU patients, day of initial application and at either 12 weeks or at 100% re-epithelialization (whichever occurs first)
  - For VLU patients, day of initial application and at either 16 weeks or at 100% re-epithelialization (whichever occurs first)
- Incidence of adverse events
- Ease of use and handling of study product
- Cost effectiveness / Economic model (amount of product usage, length of treatment)
- Reimbursement access

4. PATIENT SELECTION

4.1 Enrollment Criteria for Patients with Diabetic Foot Ulcers (DFUs)

Patients must meet all inclusion criteria and no exclusion criteria in order to be enrolled and randomized to a study product. If the patient has more than one DFU, then each DFU must meet the criteria in order for that DFU to be enrolled.

4.1.1 Inclusion Criteria for DFUs

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(s) must be located at least in part on the foot or ankle

6. Ulcer(s) must be present for more than 28 days prior to randomization and initial application of study product, and has not adequately responded to conventional ulcer therapy

7. Wound size must be >1.0 cm^2 and < 25 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(ies), 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(s) with results ≥40mmHg, OR

    b. Ankle-Brachial Index (ABI) of study leg(s) with results of ≥ 0.7 and ≤ 1.3, OR

    c. Toe-Brachial Index (TBI) of study extremity(ies) with results of ≥ 0.5

4.1.2 Exclusion criteria for DFUs

1. Patient has been previously enrolled into this study, or is currently participating in another prospective 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(s) or study wounds are less than 3 cm apart

7. Hgb A1c > 12% within 3 months prior to randomization

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(s) 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 or unable to safely utilize appropriate offloading device to unweight wound(s)

16. Study ulcer(s) experiences greater than 30% reduction over the 2-week run-in period

17. Patient also has a venous leg ulcer that is enrolled into this study

4.2 Enrollment Criteria for Patients with Venous Leg Ulcers (VLUs)

Patients must meet all inclusion criteria and no exclusion criteria in order to be enrolled and randomized to a study product. If the patient has more than one VLU, then each VLU must meet the criteria in order for that VLU to be enrolled.

4.2.1 Inclusion Criteria for VLUs

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 peripheral venous disease per investigator judgment or diagnostic confirmation

5. Ulcer(s) must be venous in origin, located on a lower extremity

6. Ulcer(s) must be present for more than 28 days prior to randomization and initial application of study product, and has not adequately responded to conventional ulcer therapy

7. Wound(s) size must be >1.0 cm^2 and < 50 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(ies), 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(s) with results ≥ 40mmHg, OR

    b. Ankle-brachial index (ABI) of study leg(s) with results of ≥ 0.7 and ≤ 1.52, OR

    c. Toe-Brachial Index (TBI) of study leg(s) with results of ≥ 0.5, OR

    d. Doppler arterial waveforms, which are triphasic or biphasic at the ankle of the affected leg(s)

4.2.2 Exclusion Criteria for VLUs

1. Patient has been previously enrolled into this study, or is currently participating in another prospective 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 known allergy to bovine materials or agarose shipping materials

5. Patient has a life expectancy less than six months as assessed by the investigator

6. Patient has received skin substitutes during the run-in period or within 14 days prior to the beginning of the run-in period

7. Patient has an additional wound within 3 cm of the study wound or study wounds are less than 3 cm apart

8. Hgb A1c > 12% within 3 months prior to randomization in patients with a known history of diabetes

9. Patient is not in reasonable metabolic control in the judgment of the investigator

10. Patient has a known history of poor compliance with medical treatments

11. Patient currently undergoing cancer treatment

12. Patient has been diagnosed with at least one of the following autoimmune connective tissue diseases: lupus, vasculitis, sickle cell, or uncontrolled rheumatoid arthritis

13. 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.

14. Active infection, undrained abscess, or critical colonization of the wound(s) with bacteria in the judgment of the investigator

15. Patient unwilling or unable to tolerate use of compression therapy for the duration of the study

16. Study ulcer(s) experiences greater than 30% reduction over the 2-week run-in period

17. Patient also has a diabetic foot ulcer that is enrolled into this study

5. STUDY CONDUCT

5.1 Schedule of Events for Diabetic Foot Ulcer (DFU) Patients:

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)	Six-Month Telephone Follow-Up (2)
	Start	7 days (± 3 days)	0	1	2	3	4	5 (3)	6	7	8	9 (3)	10	11	12	2 weeks after each wound closure (± 3 days)	Six-Months After Week 0 (± 1 month)
Informed consent	X																
Screening	X	X	X														
Demographics and history	X																
HbA1c	X(4)																
Vascularization (ABI, TBI or TcPO2)	X(4)																
Assessment of re-epithelialization				X	X	X	X	X	X	X	X	X	X	X	X	X (2)	
SF-36 Questionnaire and Pain Scale			X												X (5)		
Randomization			X														
Visual examination of wound(s) and imaging with eKARE inSight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (2)	
Product application with Restrata			X		X		X		X		X		X		X		
Standard of Care			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)	X (2)
Telephone follow-up																	X (2)

Notes:

- X – Requirement completed during patient encounter
- (1) – Treatment period visits will cease after 100% re-epithelialization of all study wounds is confirmed.
- (2) – An in-person visit two weeks (± 3 days) after 100% re-epithelialization is first identified, and a telephone call six months (± 1 month) after Week 0 are required for patients with 100% wound re-epithelialization of at least one wound. These visits are NOT required if there is not 100% re-epithelialization of any wound at or before 12 weeks.
- (3) – Weeks 5 and 9 may be conducted virtually at the discretion of the investigator and based on the evaluator's assessment at Weeks 4 and 8. A visual wound assessment and wound imaging are not required if the visit is virtual. If the patient is randomized to SOC, then SOC would not be applied during a virtual visit (at the physician's discretion).
- (4) – HbA1c and a vascularization assessment can be completed anytime within 60 days prior to Week 0
- (5) – SF-36 Questionnaire and Pain Scale will be completed during the visit when 100% re-epithelialization of all wounds is first identified or at 12 weeks (whichever occurs first)

5.2 Schedule of Events for Venous Leg Ulcer (VLU) Patients

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 16 is (± 3 days)																	Two-Week In-Person Follow-Up (2)	Six-Month Telephone Follow-Up (2)
	Start	7 days (± 3 days)	0	1	2	3	4	5 (3)	6	7	8	9 (3)	10	11	12	13	14	15	16	2 weeks after each wound closure (± 3 days)	Six-Months After Week 0 (± 1 month)
Informed consent	X																				
Screening	X	X	X																		
Demographics and history	X																				
HbA1c	X(4)																				
Vascularization (ABI, TBI, TcPO2, or DUS)	X(4)																				
Assessment of re-epithelialization				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SF-36 Questionnaire and Pain Scale																			X (5)		
Randomization			X																		
Visual examination of wound(s) and imaging with eKARE inSight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (2)	
Product application (for both assignments)			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	X	X	X	X (2)	X (2)
Telephone follow-up																					X (2)

Notes:

- -
- X – Requirement completed during patient encounter (1) – Treatment period visits will cease after 100% re-epithelialization of all study wounds is confirmed.
- (2) – An in-person visit two weeks (± 3 days) after 100% re-epithelialization is first identified, and a telephone call six months (± 1 month) after Week 0 are required for patients with 100% re-epithelialization of at least one wound. These visits are NOT required if there is not 100% re-epithelialization of any wound at or before 16 weeks.
- (3) – Weeks 5 and 9 may be conducted virtually at the discretion of the investigator and based on the evaluator's assessment at Weeks 4 and 8. A visual wound assessment and wound imaging are not required if the visit is virtual.
- (4) – HbA1c (for patients with a known history of diabetes) and a vascularization assessment can be completed anytime within 60 days prior to Week 0
- (5) – SF-36 Questionnaire and Pain Scale will be completed during the visit when 100% re-epithelialization of all wounds is first identified or at 16 weeks (whichever occurs first)

5.3 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 comparison product (Apligraf).

5.4 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.

5.5 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(s) has not decreased in size by more than 30%. Written informed consent must be obtained prior to or at the beginning of the run-in period.

More than one wound per patient may be screened, enrolled and randomized to a study product. All wounds screened/enrolled must be either DFUs or VLUs. A patient may not have both a DFU and VLU that are screened and randomized to a study product. If more than one wound is enrolled, then the wounds must be at least 3 cm apart. Additionally,

the run-in period will begin on the same day for all wounds. A patient may not have a separate run-in period for each wound.

5.5.1 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 42 days
- If vascularization in the study leg(s) 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(s)
    - Toe-brachial index (TBI) of study extremity(ies)
    - TcPO2 of study leg(s)
    - Doppler waveform of study leg(s) (VLU patients only)
- Assessment of ulcer(s) size via the eKare inSight platform according to the eKare in Sight instructions. If debridement is completed during this visit, then the assessment must be completed after debridement.
- Assessment of wound(s) 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. If a patient has more than one wound that is screened, then wound(s) that do not continue to meet all inclusion/exclusion criteria will not be randomized to a study product.

5.5.2 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(s) size via the eKare inSight platform according to the eKARE in Sight instructions. If debridement is completed during this visit, then the assessment must be completed after debridement.

- Assessment of wound(s) 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. If a patient has more than one wound that is screened, then wound(s) that do not continue to meet all inclusion/exclusion criteria will not be randomized to a study product.

5.6 Point of Enrollment

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

- Written informed consent is provided
- For patients with a DFU(s), the patient meets all DFU inclusion criteria and no DFU exclusion criteria
- For patients with a VLU(s), the patient meets all VLU inclusion criteria and no VLU exclusion criteria
- The patient has completed the 2-week run-in period with < 30% reduction in wound(s) size
- The patient is randomized

5.7 Randomization

The randomization process will be pre-programmed into the electronic data capture (EDC system) 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 with a DFU(s) will be randomized to receive either synthetic hybrid-scale fiber matrix (treatment group) or SOC (control group). Patients with a VLU(s) will be randomized to receive either synthetic hybrid-scale fiber matrix (treatment group) or living cellular skin substitute (control group).

Randomization will be stratified by wound size:

- DFUs will fall into two groups (>1.0 cm^2 and < 12.5 cm^2) and (≥ 12.5 cm^2 and < 25 cm^2). Patients within each group will be randomized in a 1:1 ratio to receive either synthetic hybrid-scale fiber matrix or SOC.
- VLUs will fall into two groups: (>1.0 cm^2 and < 25 cm^2) and (≥ 25 cm^2 and < 50 cm^2). Patients within each group will be randomized in a 1:1 ratio to receive either synthetic hybrid-scale fiber matrix or living cellular skin substitute.

Once the patient is ready to be randomized, the randomization form will be completed by study personnel in the electronic data capture (EDC) system. The randomization assignment will be obtained from the EDC system prior to the initial application of the study product. If a patient has more than one wound that meets all enrollment criteria, then all wounds will be randomized to the same study product. The largest wound that meets enrollment criteria will determine the size stratification for the patient.

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.

5.8 Activities for Research Personnel

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The following summarizes activities for research personnel from the time of enrollment/randomization through the remainder of the study. See the Schedule of Events Table for additional details.

- The **Evaluator(s)** will complete the following activities:
  - Informed consent
  - Screening assessments
  - Before randomization: administration of the SF-36 Questionnaire and pain scale
  - Before randomization: obtain images of wound(s) via the eKARE inSight Platform
  - Before randomization: assessment of wound(s) through gross observation and analysis for signs of infection, wound progression, and tissue healing
  - Before randomization: wound care including debridement and dressing changes

- Review of wound image(s) during the treatment period for 100% re-epithelialization
  - At Weeks 4 and 8: specify whether or not the patient is likely to have 100% re-epithelialization within the next week so that the investigator can determine whether Weeks 5 and 9 will be completed virtually or in-person. See Section 5.12 for additional details.
  - Review of wound image(s) at follow-up visit two weeks after 100% re-epithelialization to verify wound closure
-
  - Obtain randomization assignment
  - After randomization: obtain images of wound(s) via the eKARE inSight Platform
  - After randomization: assessment of wound(s) through gross observation and analysis for signs of infection, wound progression, and tissue healing
  - Initial application and re-application of study product

- After randomization: wound care including debridement and dressing changes
- After randomization: assessment of adverse events and medications
- After randomization: administration of the SF-36 Questionnaire and pain scale
- Virtual visits at Weeks 5 and 9, if conducted
- Telephone call six-months after initial product application to verify wound closure, drainage, and need for additional dressing

5.9 Treatment Week 0

An in-person visit will be completed 14 to 17 days after the beginning of the run-in period.

The following will be completed PRIOR TO randomization:

- Verify that the patient has active insurance.
- Review of the patient's medical history
- Assessment of medications including steroid use
- Assessment of Quality of Life - SF-36
- Pain Scale
- Assessment of wound(s) for signs of infection, wound progression, and tissue healing. Gross observation will be utilized to determine the necessity of standard dressing change.
- After initial debridement, assessment of ulcer size via the eKARE Insight platform according to the eKARE in Sight instructions. Document whether or not the ulcer size has decreased by < 30% since the beginning of the run-in period. If more than one ulcer is screened for the study, then only ulcers that have decreased in size < 30% may be randomized.

After the eKARE Insight assessment is complete, review all inclusion/exclusion criteria to verify the patient is eligible for enrollment and randomization. **Once all criteria is confirmed, the patient will be randomized.** If the patient does not meet all inclusion/exclusion criteria, then the patient will be considered a screen failure, and a study exit CRF shall be completed. If the patient has more than one ulcer that has been screened, ulcers that do not meet all inclusion/exclusion criteria will not be randomized and should receive treatment according to standard of care. All ulcers that meet enrollment criteria will be treated with the same study product beginning on the same day.

Before the patient is randomized, blinded evaluators should leave the area within view of the patient. Study product will then be applied by **study personnel**.

5.9.1 Application of synthetic hybrid-scale fiber matrix

Follow the instructions below for patients receiving synthetic hybrid-scale fiber matrix.

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 based on the eKARE inSight measurements.
- ***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 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.

A non-adherent primary dressing will be applied to the wound bed. Management of wound exudate will determine the required dressing. The dressing will be securely in place and dressing determined by provider preference.

5.9.2 Application of Living Cellular Skin Substitute (VLU Patients Only)

Follow the living cellular skin substitute instructions for use (IFU) in Appendix C for VLU patients randomized to this group. Post-application, cover living cellular skin substitute using a non-adhesive primary dressing. Apply a secondary non-occlusive dressing to create a bolster.

5.9.3 Post-Application Procedures

- Assessment of adverse events
- **For DFUs:** To ensure off-loading, each patient will be fitted with an off-loading device based on the investigator's decision, e.g., a boot for forefoot and a heel protector for hindfoot. Patients should be instructed on how to care for the surgical site, utilize an off-loading device, and keep the surgical site moist and clean. If the wound is dry, a hydrogel category dressing type should be used. If the wound has exudate, an aliginate or foam dressing is recommended.
- **For VLUs:** Patients will be provided with a compression device. Patients should be instructed on how to care for the surgical site, utilize compression socks and/or compression wrap, e.g., ProFore or a similar product, and keep the surgical site moist, and clean.

5.10 Study Treatment Period - For synthetic hybrid-scale fiber matrix and comparison products

Patients will have weekly visits for up to 12 weeks for patients with DFUs and up to 16 weeks for patients with VLUs (the window for all of these visits is ± 3 days). Assessment and imaging of the wound(s) will occur at each weekly visit unless the visit is conducted virtually (optional for Weeks 5 and 9). Assessment of adverse events and medications will be occur during each weekly visit.

Study product will be re-applied:

- **DFU patients:**
  - **Randomized to Restrata: Biweekly (weeks 2, 4, 6, 8, 10, and 12)**
  - **Randomized to Standard of Care: Weekly**
- **All VLU patients: Biweekly (weeks 2, 4, 6, 8, 10, 12, 14 and 16)**

If 100% re-epithelialization of all study wounds is confirmed before 12 weeks for DFU patients or before 16 weeks for VLU patients, then weekly visits shall cease.

5.10.1 The **evaluator** will complete these assessments at each in-person weekly visit during the Treatment Period:

- Review of images and documentation of 100% re-epithelialization, if present

5.10.2 Personnel will administer the Quality of Life - SF-36 Questionnaire and the pain scale at the following time-point (whichever occurs first):

- When complete wound re-epithelialization of all wounds is first identified, OR
- At Week 12 for DFU patients, OR
- At Week 16 for VLU patients

5.10.3 Personnel will complete the following assessments at each weekly in-person visit:

- Assessment of wound(s) through gross observation and analysis, wound progression, and tissue healing. Gross observation will be utilized to determine the necessity of standard dressing change. Carefully assess the wound(s) for signs of infection, description of exudate present, and wound bed characteristics.
- Assessment of adverse events and medications
- Debridement and dressing changes may occur at each weekly visit or as needed.
  - Debride the wound(s) as needed while not disrupting healing tissue.

- The clinician will inspect the wound bed for signs of infection and healing; the secondary dressing is changed as appropriate with a nontoxic solution. Frequency of secondary dressing changes will be dependent upon the volume of exudate produced, type of dressing used and the clinician's decision upon inspection of the wound(s).

- Measurement and imaging of wound area via the eKare inSight platform according to the eKare inSight instructions. If debridement is completed during this visit, then the assessment must be completed after debridement.

5.10.4 Reapplication of the study product by personnel will occur:

- **DFU patients:**
  - **Randomized to Restrata: <u>Biweekly up to 12 weeks</u>**
  - **Randomized to Standard of Care: <u>Weekly up to 12 weeks</u>**

- **All VLU patients: <u>Biweekly up to 16 weeks</u>**

If 100% re-epithelialization is confirmed before 12 weeks for DFU patients or before 16 weeks for VLU patients, then re-application shall cease. For patients with more than one wound randomized to the study, re-application of product to each wound shall cease when 100% re-epithelialization of that wound is confirmed. The following will be completed by qualified personnel:

- Evaluate the amount of study product remaining in the wound.
- If the study product is completely intact (no resorption has occurred) and the wound is clean and clear of infection, then leave the product in place.
- The study product should be reapplied over previously absorbed material.
- If any of the study product material has resorbed, then evaluate for additional debridement prior to replacement with new study material.
- 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 re-injury.

NOTE: If excess exudate collects under Synthetic hybrid-scale fiber matrix, the material should be thoroughly fenestrated to allow the exudate to drain.

5.11 3D Wound Measurement with the eKare inSight Platform

Wounds will be measured using the eKare inSight platform weekly from the beginning of the run-in period until 12 weeks for DFU patients or 16 weeks for VLU patients (except Weeks 5 and 9 if conducted virtually). If 100% re-epithelialization of all wounds is confirmed before 12 weeks for DFU patients or before 16 weeks for VLU patients, then

measurements shall cease. Qualified personnel who are trained on the system will be required to complete the assessment. **If debridement is completed at the visit, then the measurement must occur <u>after</u> debridement.**

The inSight platform uses structured light to produce three-dimensional renderings of wounds and translates the data into area, length, width, depth and volume within seconds.

Each investigational site will be provided with one system, which will need to be returned to the Sponsor at study conclusion.

5.12 Virtual Visits at Weeks 5 and 9

Based on the evaluator's assessment of the wound image and at discretion of the investigator, Week 5 and Week 9 may be conducted virtually (via telephone call or web meeting) by un-blinded study personnel. A visual wound assessment and wound imaging via the eKARE inSight platform are not required if the visit is virtual. If a DFU patient was randomized to Standard of Care, then product reapplication is not required if the visit is virtual. The following will be completed during virtual visits:

- Collect information about adverse events and medications
- Collect information about wound drainage and dressing changes since the previous visit
- Discuss wound care recommendations including any needed dressing changes

At Week 4, the **<u>evaluator</u>** will complete an assessment of the wound image and determine whether or not 100% re-epithelialization is likely to occur before Week 5.

- If 100% re-epithelialization of any wound is likely to occur before Week 5 based on the blinded evaluator's assessment, then an in-person visit will be completed at Week 5.
- If 100% wound re-epithelialization is unlikely to occur before Week 5 based on the blinded evaluator's assessment, then the investigator will determine whether Week 5 will be completed virtually or in-person based on the patient's best interest. For DFU patients randomized to Standard of Care, a visit may be conducted virtually only if the investigator determines it is in the patient's best interest to forego product reapplication at Week 5.

At Week 8, the **<u>evaluator</u>** will complete an assessment of the wound image and determine whether or not 100% re-epithelialization is likely to occur before Week 9.

- If 100% re-epithelialization of any wound is likely to occur before Week 9 based on the evaluator's assessment, then an in-person visit will be completed at Week 9.
- If 100% re-epithelialization is unlikely to occur before Week 9 based on the evaluator's assessment, then the investigator will determine whether Week 9 will be completed virtually or in-person based on the patient's best interest. For DFU patients randomized to Standard of Care, a visit may be conducted virtually only if the investigator determines it is in the patient's best interest to forego product reapplication at Week 9.

5.13 Two Week Visit to Confirm Wound Closure

An in-person visit with the patient to confirm 100% re-epithelialization will be completed two weeks (± 3 days) following the visit when 100% re-epithelialization was first identified and documented. A clinic visit is NOT required if there is not complete wound re-epithelialization of any wound at 12 weeks or earlier for DFU patients (or 16 weeks or earlier for VLU patients). For patients with more than one wound, an in-person follow-up visit will be completed two weeks following 100% re-epithelialization of each wound.

Research personnel will complete the following:

- Measurement and imaging of wound area via the eKare inSight platform according to the eKare inSight instructions.
- Wound drainage since the previous visit
- Additional dressing changes since the previous visit
- Adverse events
- Review wound imaging to confirm the wound remains closed

5.14 Six-Month Telephone Call

For patients with 100% re-epithelialization of at least one wound, a telephone call with the patient will be completed six-months (± 30 days) after Week 0. The following information will be collected:

- Confirmation of whether wound(s) remains closed
- Wound drainage since the previous visit
- Additional dressing changes since the previous visit
- Adverse events

A telephone call is not required if complete wound re-epithelialization of at least one study wound does not occur at or before 12 weeks for DFU patients, or at or before 16 weeks for VLU patients.

5.15 Study Exit

5.15.1 Study Participation Exit Points

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

- DFU patients <u>without</u> 100% re-epithelialization of at least one study wound: at 12 weeks
- VLU patients <u>without</u> 100% re-epithelialization of at least one study wound: at 16 weeks

- Completion of six-month telephone call (for patients with 100% re-epithelialization of at least one study wound)
- Patient withdrawal
- The Investigator may withdraw the patient if he/she determines it is in the patient's best interest
- Patient lost to follow-up
- Amputation of all or part of the study limb
- Closure of study
- Patient death

5.15.2 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.

5.15.3 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.

5.15.4 Patient Death

If known, the cause of death should be documented.

5.15.5 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 EVENTS (AE)

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 clinically significant 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 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 eCRF:

- 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:
    - Infection of wound and/or area surrounding wound
    - Complete or partial amputation of lower extremity
    - Allergic reaction to a study product
    - Excessive redness, pain, swelling or blistering of wound

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. PROTOCOL DEVIATIONS

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

All deviations from the protocol should be reported on a protocol deviation eCRF, and a reason for the deviation should be noted. Additionally, the investigator (or designee) is also required to report protocol deviations to the IRB if the protocol deviations are required to be reported per the IRB reporting requirements. Deviations that impact the rights, welfare, or safety of patients shall be reported to the sponsor and IRB as soon as possible.

If Acera Surgical, Inc. becomes aware that an investigator is not complying with any part of the protocol, including signed agreements, or any conditions of approval imposed by the reviewing IRB/EC, Acera will promptly secure compliance and may suspend the investigator's participation (including enrollment at the site).

8. RISKS AND BENEFITS

For a complete list of risks and benefits that may occur with the use of approved synthetic hybrid-scale fiber matrix, Standard of Care, and living cellular skin substitute, refer to the Instructions for Use.

9. STATISTICAL CONSIDERATIONS

9.1 Hypotheses to be Tested

9.1.1 Primary Endpoints:

9.1.1.1 DFU Arm

The null hypothesis (H_0) for the primary endpoint in the DFU arm 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 noninferiority margin of -0.10 based on a one-sided Farrington & Manning test. The alternative hypothesis (H_1) is that the difference is greater than the noninferiority margin of -0.10. These can be seen in the equations below:

$$H_0: \pi_1 - \pi_2 \leq -0.10$$
$$H_1: \pi_1 - \pi_2 > -0.10$$

9.1.1.2 VLU Arm

The null hypothesis (H_0) for the primary endpoint in the VLU arm is that the difference in proportion of patients achieving 100% re-epithelialization by week 16 between the synthetic hybrid-scale fiber matrix group (π_1) and the control group (π_2) is less than or equal to the noninferiority margin of -0.10 based on a one-sided Farrington & Manning test. The alternative hypothesis (H_1) is that the difference is greater than the noninferiority margin of -0.10. These can be seen in the equations below:

$$H_0: \pi_1 - \pi_2 \leq -0.10$$
$$H_1: \pi_1 - \pi_2 > -0.10$$

9.2 Analysis Populations

<u>Intention to Treat Population (ITT)</u>

The ITT population will consist of all enrolled patients. Patients are considered enrolled after meeting the criteria specified in Section 5.6. 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.

9.3 Sample Size Calculation

9.3.1 DFU Arm

Sample size calculations were performed using a Farrington & Manning test for non-inferiority of the synthetic hybrid-scale fiber matrix group compared to the control group. Under assumptions of a closure rate of 75% for the synthetic hybrid-scale fiber matrix group, 60% for the control group, and a noninferiority margin of 10%, this results in a sample size of 44 per group (88 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 110 patients.

9.3.2 VLU Arm

Sample size calculations were performed using a Farrington & Manning test for non-inferiority of the synthetic hybrid-scale fiber matrix group compared to the control group. Under assumptions of a closure rate of 75% for the synthetic hybrid-scale fiber matrix group, 50% for the control group, and a noninferiority margin of 10%, this results in a sample size of 24 per group (48 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 60 patients.

9.4 Interim and Final Analyses

An unblinded interim assessment for sample size re-estimation (SSR) will be performed on the primary endpoint in each arm of the study by an independent statistician.

9.4.1 DFU Arm

In the DFU arm, the analysis will be conducted when 50% of the mITT population (56 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 non-inferiority, conditioned on the interim-observed difference between treatments with respect to 100% re-epithelialization rates and on the non-inferiority 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):

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

where:

$Z_{1-\alpha}$ is the (1-α)*100% percentile of the standard normal distribution (i.e., the critical value used to assess non-inferiority 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 110 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 non-inferiority at the final analysis using a non-inferiority 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 166 patients for the DFU arm. This formula

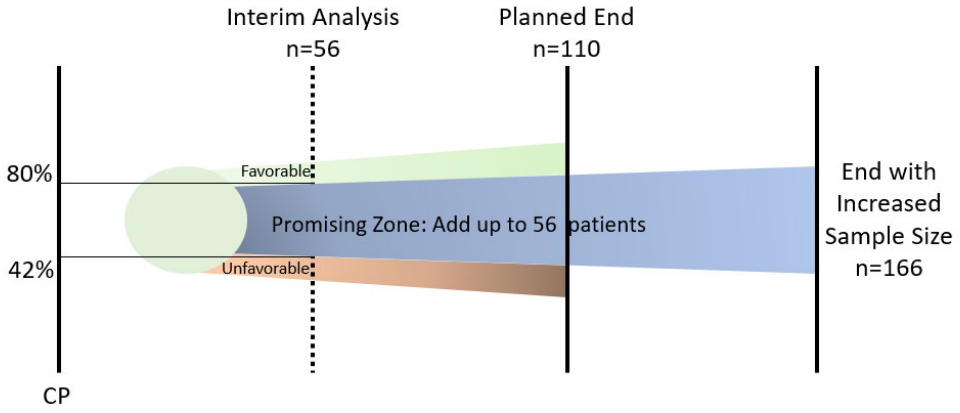
assumes the interim observed effect size between treatments is the true effect size between treatments.

Results of the interim assessment will be presented by the independent statistician to a select 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 110 enrolled patients, as scheduled.

2. If the test for conditional power is 0.42 ≤ 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 166 patients. The range 0.42 ≤ 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 166 patients or the number needed to boost CPni to 0.8.



CP=Conditional Power
Probability of success (statistical significance) at the end of the trial given current data trend

9.4.2 VLU Arm

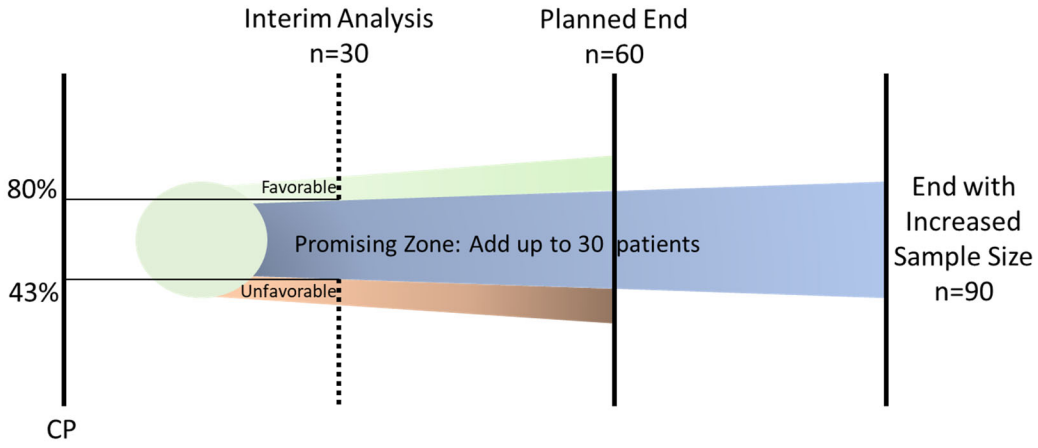
The interim analysis for the VLU arm will be performed independently of the interim analysis for the DFU arm, but it will be very similar in nature.

In the VLU arm, the analysis will be conducted when ~50% of the mITT population (30 patients) have been enrolled and completed the primary endpoint evaluation. The methods will be the same as described above. M` will not exceed 90 patients for the VLU arm.

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

1. If the test for CPni <0.43 or ≥0.8, then there is no increase in the sample size and the trial will be completed on a minimum of 60 enrolled patients, as scheduled.

2. If the test for conditional power is 0.43 ≤ 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 90 patients. The range 0.43 ≤ 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 90 patients or the number needed to boost CPni to 0.8.



CP=Conditional Power
Probability of success (statistical significance) at the end of the trial given current data trend

9.5 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 higher will be used for the statistical analysis.

9.5.1 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.

9.5.2 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.

9.5.3 Procedural Information

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

9.5.4 Primary Endpoints

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

9.5.4.1 DFU Arm

100% re-epithelialization will be assessed every week (except during virtual visits) for 12 weeks for DFU patients 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 non-inferior between groups using a Farrington & Manning test. Noninferiority 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 non-inferiority margin of -10%.

If non-inferiority is shown, superiority of synthetic hybrid-scale fiber matrix over Standard of Care will be tested using a chi-square test.

9.5.4.2 VLU Arm

100% re-epithelialization will be assessed every week (except during virtual visits) for 16 weeks for VLU patients 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 16 a Farrington & Manning test will be used. Noninferiority 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 non-inferiority margin of -10%.

9.5.5 Secondary Endpoints

The following secondary endpoints will be summarized for exploratory purposes. There are no plans for statistical testing of secondary endpoints.

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 the eKARE inSight system every week (except during virtual visits) for 12 weeks for DFU patients and 16 weeks for VLU patients (except during virtual visits), 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.

9.5.6 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. There are no planned statistical tests. 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.

Patient Reported Pain

Pain will be assessed using a numeric rating scale of 10-point scale. Results will be summarized at each time point using the average pain score and the average change from baseline.

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

Results will be summarized descriptively by timepoint where applicable.

Intraoperative notes / Ease of Use, Handling

Results will be summarized descriptively by timepoint.

Billing / Coding / Reimbursement information

Results will be summarized descriptively by timepoint.

9.5.7 Adverse Events

9.5.7.1 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.

9.5.7.2 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.

9.5.7.3 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

9.6 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. For the DFU arm, 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. Similarly for the VLU arm, the one sided Fisher's Exact 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.

10. DATA HANDLING AND RECORD KEEPING

Electronic Case Report Forms (eCRFs)

Completed original eCRFs are the sole property of Acera Surgical, Inc. 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 eCRFs by the clinical research team and to review and approve the data captured on all eCRFs as accurate. All eCRFs must be signed by the investigator. This signature serves to attest that the information contained on the eCRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all data entered on eCRFs. Patient source documents are the investigator's patient records maintained at the study site and will be used to verify data documented on eCRFs.

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

Source Documents

Investigators are required to maintain information in the study patient's medical records to corroborate data collected on the eCRFs. Source data includes all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of source documents are: hospital medical records, clinic and office medical charts, laboratory notes, imaging, patient questionnaires and study worksheets.

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.

11.ETHICS

11.1 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.

11.2 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.

11.3 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.

12.MONITORING

Site monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with applicable regulations, agreements with the sponsor, the currently approved protocol, and with any requirements imposed by the IRB.

Monitoring will be performed by the sponsor and/or its representatives, and monitors will be qualified by training and experience. On site and/or remote visits will be made before the study begins, at regular intervals during the study, and at the study closeout. The purpose of visits will be to:

- Provide study training
- Verify adherence to the protocol, agreements, IRB requirements, and applicable regulations
- Review essential study documentation including site personnel documents, study logs and IRB correspondence
- Verify informed consent was properly obtained
- Verify the completeness and accuracy of source documentation and eCRFs

13.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.

13.1 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.

13.2 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

13.3 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.

14. 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.

15. SUMMARY OF PROTOCOL REVISIONS

Revision Number	Date	Sections Revised	Summary of Changes

01	27 January 2021	N/A	N/A – Initial Version
02	08 March 2021	Section 1 Section 5.15.1	Removed National PI and Added Steering Committee Added the following study participation exit point: the Investigator may withdraw the patient if he/she determines it is in the patient's best interest
03	30 September 2022	Section 1, 2.2, 2.4.1, 3, 4.1.2, 5.1, 5.3, 5.7, 5.9, 5.9.2, 5.10, 5.10.4, 5.12, 8, 9.5.4.1, and 15	Removed Lyophilized Fish Skin (Kerecis) as a comparator for DFU Removed references to blinding Added Standard of Care (SOC) as a comparator for DFU

16. REFERENCES

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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.

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5. 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

6. 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.

7. Apligraf. (2020). https://apligraf.com

17. APPENDICES

Appendix A: Synthetic Hybrid-Scale Fiber Matrix (Restrata) Instructions For Use

Appendix B: Standard of Care (Instructions)

To ensure off-loading, each patient will be fitted with an off-loading device based on the investigator's decision, e.g. a boot for forefoot and a heel protector for hindfoot. Patients is instructed on how to care for the surgical site, utilize an off-loading device, and keep the surgical site moist and clean. If the wound is dry, a hydrogel category dressing type should be used. If the wound has exudate, an alginate or foam dressing is recommended.

Appendix C: Living Cellular Skin Substitute (Apligraf) Instructions for Use