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Sponsor:

CellTherX Corporation

2929 Carlisle Street, Suite 170
Dallas, TX 75204

Protocol Number:

MB2019-01

Official Title:

A PROSPECTIVE, RANDOMIZED STUDY TO EVALUATE THE EFFECTIVENESS OF MICROSURFACED VS CONTROL CADAVERIC DECELLULARIZED GRAFTS TO ESTABLISH WOUND BED PREPAREDNESS IN DEEP PARTIAL AND FULL-THICKNESS BURN WOUNDS

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Note: The date on the Title Page, Signature pages, and listed in the header is the date of compilation and not of an update to or approval of content.

A Prospective, Randomized Study to Evaluate the Effectiveness of Microsurfaced vs Control Cadaveric Decellularized Grafts to Establish Wound Bed Preparedness in Deep Partial and Full-Thickness Burn Wounds

Protocol Number:
MB2019-01

Sponsor:
[redacted]

Primary Study Correspondent:
Kathryn Davis, PhD
[redacted]

Issue Date:
July 1, 2021

SPONSOR SIGNATURE PAGE

A PROSPECTIVE, RANDOMIZED STUDY TO EVALUATE THE EFFECTIVENESS OF MICROSURFACED VS CONTROL CADAVERIC DECELLULARIZED GRAFTS TO ESTABLISH WOUND BED PREPAREDNESS IN DEEP PARTIAL AND FULL-THICKNESS BURN WOUNDS

PROTOCOL NUMBER:
MB2019-01

SPONSOR:
[redacted]

PRIMARY STUDY CORRESPONDENT:
KATHRYN DAVIS, PHD
[redacted]

ISSUE DATE:
July 1, 2021

Print Name, Title, Company: _____

Signature: _____ Date: _____

INVESTIGATOR SIGNATURE PAGE

A PROSPECTIVE, RANDOMIZED STUDY TO EVALUATE THE EFFECTIVENESS OF MICROSURFACED VS CONTROL CADAVERIC DECELLULARIZED GRAFTS TO ESTABLISH WOUND BED PREPAREDNESS IN DEEP PARTIAL AND FULL-THICKNESS BURN WOUNDS

PROTOCOL NUMBER:
MB2019-01

SPONSOR:
[redacted]

PRIMARY STUDY CORRESPONDENT:
KATHRYN DAVIS, PHD
[redacted]

ISSUE DATE:
JULY 1, 2021

Site Name: Joseph M. Still Burn Center at Doctors Hospital Augusta

Print Investigator Name: _____

Investigator Signature: _____ Date: _____

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Primary Study Contacts

SITE

Principal Investigator	Zaheed Hassan, MD
email	[redacted]
phone	706.364.2966
Primary Contact	Joan Wilson, MSN, MHA, RN
email	joan.wilson@jmsresearchfoundation.org
phone	706.364.2966

[redacted]

Medical Lead	Kathryn Davis, PhD
email	[redacted]
phone	[redacted]

Executive Summary

Title of Study	A Prospective, Randomized Study to Evaluate the Effectiveness of Microsurfaced vs Control Cadaveric Decellularized Grafts to Establish Wound Bed Preparedness in Partial and Full-Thickness Burn Wounds
Protocol Number	MB2019-01
Study Purpose	This study will be performed in 2 phases. The first phase is to test the clinical efficacy of Microsurfaced cadaveric decellularized grafts to establish burn wound healing in partial-thickness burns and wound bed preparedness in deep-partial and full-thickness burn wounds as compared to Control Cadaveric Grafts over a 6-week treatment period. During the treatment period, each burn site will be monitored readiness to graft. In the second phase, autograft percent take and outcomes will be assessed during a follow up phase. Additionally, cost effectiveness will be assessed between the treatment groups to establish which treatment achieves time to grafting sooner.
Study Design	Prospective, randomized, single subject design pilot clinical trial.
Enrollment	Twenty (20) subjects will complete the study.
Investigational Sites	Joseph M. Still Research Foundation
Study Duration	Up to 12 months
Efficacy Endpoints	Primary Endpoint (Part A): To compare wound bed preparedness/time to autograft in deep-partial and full thickness burns in burn sites treated with Microsurfaced vs Control cadaveric graft-treated groups through 6 weeks post initial injury. Secondary Endpoints (Part B): To compare the incidence of the outcome noted below at the burn site treated with Microsurfaced vs Control cadaveric graft-treated groups. 1. Incidence of Infection at each treatment study visit 2. Change in tissue oxygenation at study burn site at the time of autografting as compared to baseline. 3. Autograft take and tissue oxygenation change over time during 2 week observation. 4. Tissue oxygenation, and scar assessment outcomes at 3, 6, 9, and 12 months.
Safety Endpoints	The incidence of events reported
Study Groups	Study burn sites (2) within each subject will be randomized to be treated with Microsurfaced or Control cadaveric grafts.

1. Introduction

Background and Rationale

Allogenic and xenogenic skin has been used as temporal biologic dressings on excised wounds for many years, and the application of allograft on large-surface excisional wounds has contributed to a documented increase in survival rates in large burns [1, 2]. If autograft is not an option due to lack of donor skin, prompt coverage of the excised burn wound with allograft will protect the debrided area, prevent fluid losses, and promote vascular ingrowth that will optimize future autograft take [3]. Subsequent removal of the adherent allograft skin results in a well-vascularized wound bed that is suitable for autografting. Fresh and cryopreserved skin maintain the highest biologic properties (e.g., adherence to the wound bed) [4].

[redacted] [redacted] hypothesizes that adding microsurfacing to the dermal side of the graft will promote better healing outcomes by increasing graft surface area and improving adhesion of the graft to host tissue. This interface/adhesion is critical for optimal wound bed preparation as the contact between graft to host promotes fibrovascular ingrowth of tissue as well as protecting the wound bed from bacterial infection [5-7]. Microsurfacing is performed using a biologic cutting die that is used for cutting biologic tissues to shape/size. The [redacted] Surfacing Device, based on BioCut Systems SterilCut 7T Bio-Format Pneumatic Press (Milwaukee, WI), is used to make partial cuts through the tissue to create cutting patterns that can be varied from denser (left) to less dense (right) as shown in Figure 1.

Figure 1. Dermal Microsurfacing

Summary of Findings from Previous Studies

Recently performed studies (unpublished) using a porcine model demonstrated that microsurfacing grafts resulted in increased cellular response in the center of the grafts. Increased levels of CD3, Factor VIII, and vimentin, demonstrated improved blood flow, growth factor recruitment and fibroblast proliferation to the microsurfaced graft. These data would suggest that microsurfacing cadaveric grafts may demonstrate better healing outcomes as compared to control grafts.

Device Description

Frozen Cadaveric Decellularized STSG (Control)

Cryopreserved cadaveric decellularized split thickness skin grafts (dSTSG) are human allografts comprised of the epidermal layer of tissue and a thin layer of dermis that lends structure and support. It is intended for the temporary coverage of acute burn wounds, and is available in a variety of sizes, and in both meshed and non-meshed configurations. Meshed grafts and non-meshed grafts will be used for this study. It performs the life-saving functions of the patient's own skin, including control of evaporative fluid loss, regulation of body temperature, and minimalization of contamination, until the burn is able to be covered with a permanent autograft. For this study, the Control STSG will be Maxxeus Allograft (Community Tissue, Ft Worth, TX).

Microsurfaced Cadaveric Decellularized STSG (Active)

The cryopreserved cadaveric dSTSG (non-meshed, to be meshed after microsurfacing is performed) will be microsurfaced using a proprietary technique developed by [redacted] creating a consistent microsurfacing pattern over the entire dermal surface of the graft. The processes of microsurfacing tissue are performed in stages. One such method of tissue microsurfacing is performed in the Tissue Bank facility clean room:

1. By means of software analysis of the tissue, a desired computer-generated template is created with a multitude of horizontal, vertical, and diagonal lines.
2. The computer-generated template is and transferred to a recipient Biocut tool die cutting device
3. During the clean room tissue processing, the computer-generated template will then create partial thickness cuts of various depths/widths by means of the Biocut tool die
4. The use of computer-generated templates facilitates creating a consistent and controlled microsurfacing of the dermal side of the dSTSG
5. Using the Tissue Bank's standard procedures, the dSTSG graft undergoes processing to a final product.

Regulatory Status

[redacted] recently solicited a Regulatory Review of their tissue microsurfacing process from NAMSA. The letter states the below conclusion and is attached as Appendix A.

Devices Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Guidance for Industry and FDA Staff (July 2007), provides: "Devices intended to process HCT/Ps ex vivo to create a therapeutic article, that is, products where the intended therapeutic effect is mediated by the biologic output of the device, have been assigned to CBER. For example, devices that produces autologous stem cells or hematopoietic progenitor cells for in vivo use have been assigned to CBER for review under the device provisions of the Federal Food, Drug, and Cosmetic Act (the Act), or the Public Health Service (PHS) Act. Similarly, devices that process autologous blood or tissue to produce a new HCT/P (e.g., a tissue engineered, live cell construct) at the point of care, for direct re-administration to that patient have also been assigned to CBER for review."

Conclusion: The tissue microsurfacing process is performed by a device that does not produce a therapeutic effect as mediated by biological output of the device, nor does it process a new HCT/P. Thus, it does not fall under the guidance regulation and is not considered to be a medical device.

Benefits and Risks

Potential Benefits to the Subjects

There is no promise or guarantee that microsurfaced cadaveric grafts will improve the time to prepare the subject's wound for autografting, however preclinical studies have suggested improved cellular response with microsurfacing. The clinical results may prove this hypothesis. Moreover, the potential benefits may extend beyond the immediate healing of burn wound. The effects of microsurfacing may strengthen the healed tissue and longer-term outcomes may be improved.

Potential Risk

Participation in this clinical investigation presents low risk to subjects. Some general risks associated with any new wound dressing or skin-contact devices are listed in the table below.

Risks	Disorders/Conditions
Skin and Subcutaneous Tissue Reaction/Allergy	• Skin rash, irritation, blistering • Pruritus/itching • Skin excoriation/breakdown • Skin scarring if significant skin irritation were to occur • Skin hyper/hypo-pigmentation at and/or around dressing application area • Erythema/redness, edema, inflammation, or swelling at and/or around dressing application area
Mild Pain or Discomfort	• Tenderness/minor ache at and/or around dressing application area • Decreased sleep or sleep quality • Paresthesia (numbness, tingling, prickling, creeping sensation)
Other	• Risks to privacy • Loss of data confidentiality

Protection Against Risks

Protected health information (PHI) of subjects in clinical investigations are kept as confidential as possible in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). However, confidentiality cannot be assured. The table below lists the entities granted access to protected health information (PHI).

Entity	Reason for Access
Sponsor's Clinical Representative (Monitor)	Assess data for accuracy and completeness
Institutional Review Board (IRB)	Ensure protection of research subjects
Regulatory Authorities (e.g. Food and Drug Administration	Audit clinical trial for Subject protection and data integrity
Investigator/Site Staff	Collection and assessment of data for accuracy and completeness

Alternatives to Participation:

Subjects are not required to participate in this research study. As an alternative to study participation, subjects will receive wound care treatment per physician discretion.

2. Trial Objectives

The objective of this trial is to evaluate change in clinical outcomes of microsurfaced cadaveric dSTSG to establish wound bed preparedness in deep-partial and full-thickness burn wounds as compared to control cadaveric dSTSG over a 6-week treatment period. During the treatment period, each burn site will be monitored readiness to graft. Followup visits will be performed at 3, 6, 9, and 12 months to assess percent autograft take and adverse events and to photograph and assess scar.

3. Selection and Withdrawal of Subjects

Inclusion Criteria:

- Signed informed consent by patient or Legally Authorized Representative (LAR)
- Subject with deep partial or full thickness burn injury due to flame burn, scald injury or contact burn
- Study burn site large enough to accommodate placement of control and microsurfaced cadaveric graft (minimum 4 cm^2 each) at the same location OR 2 study burn sites large enough to each accommodate control and microsurfaced cadaveric graft, respectively at minimum 4 cm^2.
- Total Body Surface Area burned (TBSA) total ≤30 %
- Admission within 72 hours of burn injury
- Non-infected wound as diagnosed by the attending physician upon admission
- Treated as an outpatient or in an observational setting

- 21 years of age or older

Exclusion Criteria:

- Burns involving the face
- Causes other than contact burn, flame or scald injuries (i.e., electrical, chemical or frostbite)
- Admission time greater than 72 hours after the injury
- Wounds noted to be infected at admission
- Is pregnant or plans to become pregnant
- Is nursing or actively lactating
- Developmental disability/significant psychological disorder that in the opinion of the investigator could impair the subject's ability to provide informed consent, participate in the study protocol or record study measures, including untreated schizophrenia, bipolar disorder and psychiatric hospitalization within the last 2 years.
- Active alcohol or substance abuse in the opinion of the investigator that could impair the subject's participation in the study protocol or record study materials
- Any medical condition or co-morbidity that in the opinion of the investigator, would prevent successful participation in the study

Withdrawal of Subjects

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the PI for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject, per institutional protocol. In any circumstance, every effort should be made to document subject outcome. The Investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AE's.

Any related SAE occurring within 14 days following subject discontinuation must be reported to [redacted] and be followed up until stabilization or resolution. If the Subject withdraws from the study, and also withdraws consent for disclosure of future information, no further study evaluations will be performed, and no additional data will be collected. The PI may retain and continue to use any data collected before such withdrawal of consent.

The Investigator may choose to withdraw their own participation or discontinue a Subject from study with or without their consent for any of the following:

- Adverse Events
- Non-compliance
- Safety

- Complications
- Unforeseen events

A patient who experiences the noted changes, relative to previous measures, in the following parameters will be terminated early from study participation

- An increase in wound size by 50% or more prior to debridement.
- Presence of infection that in the opinion of the PI requires treatment outside the study scope
- Need for wound management outside the study scope
- Or for any reason that may, in the opinion of the Investigator, affect negatively the wellbeing of the subject.

If for any reason the subject is withdrawn from the clinical investigation, the Investigator will inform the subject accordingly.

4. Trial Design

Description of Trial Design

This study is designed as a prospective, randomized, within subject controlled design to evaluate the effectiveness of Microsurfaced vs Control cadaveric grafts for coverage of acute deep-partial or full-thickness burn wounds to promote wound healing. This study will be performed in 2 parts: Time to wound bed preparedness through 6 weeks (Part A) and wound site healing, graft take and long-term scar outcomes (Part B). Subjects will be treated with both control and microsurfaced cadaveric grafts on adjacent deep-partial or full-thickness burn wounds.

Trial Endpoints

Primary Endpoint (Part A): To compare wound bed preparedness/time to autograft in deep-partial and full thickness burns and burn wound healing in partial thickness burns in burn sites treated with Microsurfaced vs Control cadaveric graft-treated groups through 6 weeks post initial injury.

Secondary Endpoints (Part B): To compare the incidence of the outcome noted below at the burn site treated with Microsurfaced vs Control cadaveric graft-treated groups.

1. Incidence of Infection at each treatment study visit
2. Change in tissue oxygenation at study burn site at the time of autografting as compared to baseline.
3. Autograft take and tissue oxygenation change over time during 2 week observation.
4. Tissue oxygenation, and scar assessment outcomes at 3, 6, 9, and 12 mo.

Sample Size

For this pilot study, 20 patients from Joseph M. Still Research Foundation will complete the study (no cap on enrollment).

Investigational Sites

Joseph M. Still Research Foundation

PI: Zaheed Hassan, MD
Location: Augusta, GA

Duration of Subject Participation

- Screening: Within 72 hours of burn injury
- Treatment period: Up to 6 weeks
- Total duration of subject participation: Up to 12 months

Screening and Enrollment

Patients who present to the investigator's institution (through clinic admission, direct transfer from another facility, or through the emergency room) may be recruited to participate in the study. No direct marketing for subject recruitment will be done.

Patients approached for study participation will be at least 21 years of age at the time of consent, will undergo wound assessment, and meet all eligibility requirements. Those meeting eligibility criteria for the study will have the study explained to them by the Investigator. An Informed Consent Form will be provided to sign according to Section 11 prior to undergoing any study procedures. Patients will be encouraged to ask questions of the investigators. It will be made clear to the patient that not participating in the study will in no way influence the treatment plan or the relationship with the physician.

There is no cap on the number of subjects that can be screened. Additional subjects will continue to be recruited as needed to reach the minimum number of 20 treated per protocol.

Wound Selection

Up to 2 burn sites will be included in the study and each randomized to control or microsurfaced groups. Burn sites should be similar in nature (degree of burn, anatomical site, etc). Subjects with more than 2 burn wounds will have up to 2 burn sites meeting all eligibility requirements chosen for inclusion in the study. The etiology of the chosen burn site will be documented. If a single burn site is chosen, it must accommodate $\geq$ 4 cm^2 cadaveric graft for each of control and microsurfaced grafts. If 2 study burn sites are chosen, each must accommodate $\geq$ 4 cm^2 cadaveric graft each (equivalent size cadaveric graft will be placed on each site). Control and microsurfaced grafts will be provided per subject for each graft change required). Grafts may be meshed 1:1 or 2:1 to

accommodate burn size, however sites within a single subject MUST be applied with the same meshing ratio (or unmeshed).

Randomization

Prior to study initiation, Active and Control samples will be assigned to 'A' or 'B' and placed in sealed, pre-numbered randomization envelopes will be provided to the research staff and used to obtain randomization assignment. When subjects are enrolled in the study, study staff will use the randomization number labels contained in the envelope. The number will become the subject ID. The research staff will note treatment assignment of 'A' or 'B' on the CRF (e.g. A=microsurfaced and B=control).

Visit Schedule

Study procedures for each phase of study are outlined below. In a later section, details on each study procedure are described, including equipment designation.

Screening

1. Explain purpose and nature of the study and obtain signature on the informed consent document.
2. Screen the subject against protocol inclusion and exclusion criteria, including all pertinent tests

Baseline (may be done as same day as screening procedures) and Therapy initiation

1. Obtain general medical history and demographic information and social history
2. Complete a physical examination, body weight, height, and vital signs, including measurement of resting heart rate, respiratory rate, and blood pressure while seated.
3. Select the study burn site(s)
4. Obtain complete history pertinent to burn site including cause and duration of target burn and previous and current treatment.
5. Perform debridement/excision if indicated, document level.
6. Assign burn site area to receive microsurfaced or control cadaveric graft by marking location with skin safe marker as 'A' or 'B'. Each site will be minimum 4 cm^2.
7. Perform standardized photography with a ruler in every image for each site, preferably both sites in a single view if possible.
8. Perform baseline perfusion measurements using hyperspectral imaging, being sure that both sites are captured.
9. Collect all relevant concomitant medication
10. Collect and assign randomization scheme to study site 'A' and 'B'
11. Dress burn study site with microsurfaced and control cadaveric grafts per randomization scheme and repeat standardized photography (with ruler) after dressing with identification of each dressing. Document size and meshing of allograft. Note that meshing needs to be

the same for the two study sites.

Part A: Therapy/Treatment Phase

Wound Bed Prep Visit through Week 6 (every 5-7 days):

1. Remove outer dressing and perform standardized photography with ruler.
2. Assess target burn sites and assess wound bed preparation. If a site is deemed ready for autografting, document as such, complete steps 5-8 and burn site will exit the wound bed prep phase and enter autograft take phase. Document size and meshing of autograft. Note that meshing needs to be the same for the two study sites.
3. Any site that does not achieve adequate wound bed preparation or is not ready for autografting by week 6 will be exited from the study
4. Debridement or dressing change is to be performed, if indicated, and level documented.
5. Perform standardized photography of the study sites if debridement was performed.
6. Perform hyperspectral imaging being sure that both sites are captured.
7. Collect all relevant concomitant medication
8. Assess adverse events.
9. Redress the burn with treatment cadaveric graft per randomization scheme and document size of graft placed. Apply outer dressing.

Autograft Take Visit through 2 weeks (every 5-7 days)

1. Remove outer layer dressing and observe autograft. Perform standardized photography with ruler.
2. Determine if the graft has taken (yes/no) and estimate total take (0-25%, 25-50%, 50-75%, 75-95+%). If graft is fully taken, subject will enter the follow up phase.
3. Assess any graft loss and reason for loss. Document any replacement of graft material (size).
4. Perform hyperspectral imaging being sure that both sites are captured.
5. Collect all relevant concomitant medication
6. Assess adverse events.
7. Redress the burn with treatment cadaveric graft per randomization scheme and document size of graft placed. Apply outer dressing.
8. If graft has not taken (95%+) within 2 weeks, subject is exited from the study

Part B: Followup Phase

At 3, 6, 9, 12 months (+/- 4 weeks):

1. Remove outer dressing (if present) and perform standardized photography with ruler.
2. Assess scar formation using the Patient and Observer Scar Assessment Scale (POSAS)
3. Perform hyperspectral imaging of the autograft and surrounding tissue, being sure that both sites are captured.
4. Collect all relevant concomitant medication
5. Assess adverse events.

Detailed Study Operations

Medical Status/History

- *Body Mass Index (BMI):* BMI is calculated as the ratio of body weight in kilograms (kgs) to height in meters squared (m^2).

- *Medical History:* The following information will be collected from each subject

  - Previous medical history
  - previous burn history
  - perfusion at burn site
  - dermatologic history
- history of non-healing
- vital signs (weight, height, HR, BP)
- date and type of previous surgeries

Clinical Lab Values

- Pregnancy test if indicated

Concomitant Medications

All antibiotics, antifungals and other anti-infective therapies engaged in by the subject will be recorded at screening visits and follow up visits.

Social Factors

The following social factors will be recorded:
- occupation
- tobacco use history: number of years of smoking, current or previous smoker, use of chewing tobacco, average daily number of cigarettes for current smokers
- alcohol and drug use history: current and/or previous history, types of alcohol/drugs consumed in the past and/or present; frequency and amount of alcohol/drugs consumed in the past and/or present

Demographic Variables

The following demographics will be recorded for each subject:
- Gender: male or female.
- Age
- Language Spoken: English, Spanish, English and Spanish, other (specify)
- Ethnicity: Caucasian, Hispanic, African American, American Indian, Asian/Pacific Islander.

Wound History and Assessment

- ***Burn site Evaluation:*** Burn depth will be documented on admission. Only subjects with deep-partial or full-thickness burns will be included in the study.

- ***Wound Debridement, Excision and Measurements:*** Debridement will be performed per physician discretion to remove debris, necrotic tissue, and non-viable tissue to create an optimal wound bed. All debridement procedures will be documented, and the debrided site noted. Cleaning of the burn wound will be classified as 'excised' or 'debrided' or 'none.' The depth of the debridement/excision level will be documented as "subcutaneous" or "deep." The burn sites will be photographed with a ruler in the image as standardized photography.

- ***Safety Measures:*** Each of the following measures will be rated on the following 5-point Likert scale, as well as a descriptive evaluation being recorded, as applicable, for the study wound: 1) absence or 2) presence of the following:
    - Erythema
    - Discharge/drainage
    - Malodor
    - Tissue necrosis
    - Shearing/Graft Loss – if yes note percentage of graft lost or sheared

Vascular Assessment

We will assess perfusion using Hyperspectral imaging (Kent Imaging). Evaluation of the burn site and the tissue surrounding the burn site will be performed. $Snapshot_{NIR}$ uses light in the near-infrared (NIR) spectrum that, harmlessly, passes through the skin and is reflected off the blood supplying the tissue to determine tissue oxygen saturation, a key indicator of tissue health. The NIR light has two key features that make it useful for measuring the viability of living tissue. Firstly, NIR light is not absorbed by tissue as much as visible or ultraviolet light. Secondly, NIR light is mainly absorbed by hemoglobin and water. Most importantly, the wavelength dependent light absorption of hemoglobin differs if it is carrying oxygen from when it is not. This makes NIR light very useful in detecting oxygenated and deoxygenated blood, which conveys a comprehensive picture of tissue health and the healing capacity of wounds or tissue transplants.

Tissue Harvesting

Cadaveric tissue removed from the patient at the time of healing will be cut into small pieces (at least 4 pieces of maximum $0.5cm^3$) and placed in fixative to be used for histological analyses.

Patient and Observer Scar Assessment Scale (POSAS) [8]

- Physician Global Assessment will be performed at 3, 6, 9, 12 weeks using the overall opinion question of the POSAS scale. Physicians will be asked to rate the severity of the participant's scar compared to normal skin. The overall opinion scale score ranged from 1 (normal skin) to 10 (worst imaginable scar).
- Physician scar assessment will be performed at 3, 6, 9, 12 weeks using 10-point POSAS scale. Physician will rate each of the items (vascularity, pigmentation, thickness, relief, pliability, surface area and overall opinion) for a scar on a score of 1 (normal skin) to 10 (worst scar imaginable).
- Patient Global Assessment will be performed at 3, 6, 9, 12 weeks using the overall opinion question of the POSAS scale. Participants will be asked to rate the severity of their scar compared to normal skin. The overall opinion scale score ranges from 1 (normal skin) to 10 (very different from normal skin).

Standard of Care

- Burn site Care: Dressings will be placed over the cadaveric graft (either microsurfaced or control) as well as other sites adjacent that are not a part of the study sites. Dressings over study sites will be consistent for all subjects in the study.
- Dressings will consist of non-adherent primary layer with a silver contact dressing as a secondary layer. Kerlix wrap with compression will be used per PI discretion.

Schedule of Events Table – Treatment Phase

The table below shows the schedule of planned events for each subject in this study.

Schedule of Events Table

		Visit every 4 days +/- 1 days through 6 weeks,				
	SC	**Visit Week 0 Baseline**	**Visits Week 1-5**	**Visit Week 6**	**Autograft Week 1-2**	**FUP Visits[##]**
Inclusion/Exclusion	X					
Randomization	X					
Medical History, Social, Demographics, PE, Vitals		X				
Lab Values		X				
Hyperspectral Imaging		X	X	X	X	X[#]
Burn Assessment, Debridement if indicated		X	X	X	X	
Burn Photography and Measurements		X	X	X	X	X
POSAS						X
Application of graft and dressing change**		X	X		X	
Adverse Events			X	X	X	X
Concomitant Medication			X	X	X	X
Autograft Assessment					X	X
Stipend Disbursement						X

**study graft should only be removed and replaced per PI discretion
[#]only performed at 3 and 6 month visits
[##] at 3, 6, 9 and 12 months +/-1 month

Trial Monitoring

Monitoring visits will be conducted by representatives of [redacted] according to the U.S. CFR Title 21 Parts 50, 56, and 812 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the [redacted] contact and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

Clinical monitors, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of this study. The clinical monitor will evaluate compliance with the protocol, FDA regulations, any specific recommendations made by the investigational site's IRB and the signed Investigator Agreement. Telephone, e-mail and fax communications, as well as on-site visits, will be conducted to ensure that this protocol is being followed and that any protocol deviations are properly documented. Clinical monitoring will include verification that the Informed Consent forms were properly completed for all subjects enrolled in this study, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results, reporting of complications, adverse events and unanticipated adverse device effects, and a review of source documents. The clinical monitor will verify that the Case Report Forms (CRFs) are in agreement with the source documentation and other study-related records available at the site. For record verification purposes, the clinical monitor will be provided access to relevant hospital records, original laboratory data, and other records and data as they relate to this study and as agreed to with the investigator prior to the initiation of the study. The investigator will make available to the clinical monitor for review all signed Informed Consent forms, all completed CRFs, source documentation and other relevant records for all subjects enrolled at the site. It is important that the investigator and other relevant site personnel are available for consultation with the clinical monitor during the monitoring visits and that sufficient time is devoted at the site for the monitoring process. Additionally, telephone, e-mail and fax communications will be conducted on a regular basis with the investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the course of the study. If a deficiency is noted during an on-site visit (or at any other time during the course of the study), the clinical monitor is required to discuss the situation with the investigator and the Sponsor (if required) to secure compliance.

Audits and Inspections

Internal audits are done periodically to assure regulations, guidelines and protocols are adhered to appropriately. Patient binders are reviewed for proper informed consent process documentation, case report forms are compared to the source documents and reviewed for accuracy and an independent review of the inclusion and exclusion criteria using a checklist. Additionally, the use of an auditing and monitoring tool which includes sections on consent, HIPAA, on study/treatment, off treatment/off study and a general section. Weekly meetings occur to go over each study. If there are any issues that arise, they are brought up and discussed at the meeting.

5. Assessment of Efficacy

Primary Endpoint: To compare wound bed preparedness/time to autograft in deep-partial and full thickness burns and burn wound healing in partial thickness burns in burn sites treated with Microsurfaced vs Control cadaveric graft-treated groups through 6 weeks post initial injury.

Secondary Endpoints: To compare the incidence of the outcome noted below at the burn site treated with Microsurfaced vs Control cadaveric graft-treated groups.

1. Incidence of Infection at each treatment study visit
2. Change in tissue oxygenation at study burn site at the time of autografting as compared to baseline.
3. Autograft take and tissue oxygenation change over time during 2 week observation.
4. Tissue oxygenation, and scar assessment outcomes at 3, 6, 9, and 12 mo.

6. Assessment of Safety

Primary Safety Endpoint

The incidence of adverse events reported

7. Statistics

General Statistical Considerations

The data from this study will be analyzed in 2 parts. Data from the Primary Endpoint (Part A) will be locked after the final patient completes the final Therapy/Treatment phase visit. The Followup phase will be analyzed as Part B after the last patient completes the final follow up visit.

We will summarize study variables as means and standard deviations (SD) for continuous variables and proportions or percentages for categorical variables. Continuous variables will be presented as median, mean ± standard deviation and dichotomous variables presented as percent. We will use Analysis of Variance ANOVA to test for differences in continuous variables. For categorical variables, we will use chi square to compare the proportion of outcomes in each treatment arm with an alpha of 0.05, and we will use Kaplan Meier analysis to compare healing/take rates of the treatment groups. p-values were reported using the step-up Bonferroni method of Hochberg. We used an adjusted two-sided analysis with an alpha of 0.05. In the intent to treat analysis we used the last observation carried forward to define the clinical outcomes for patients that were lost to follow up.

Sample Size Justification

No sample size justification will be performed

8. Data Management

Standardized CRFs will be provided to all participating sites. Investigators are responsible for the accurate completion and timely submission of the data collected during the trial. All data from the trial will be entered from the CRFs into a central database. Incoming data will be frequently reviewed to identify inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed with the investigator by the CRO. Quality assurance procedures will be established to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed, and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. Investigators are to maintain all source documents as required by the protocol, including laboratory results, supporting medical records, and signed Informed Consent Forms. The source documents will be used during the regular monitoring visits to verify information from the database against data contained on the completed CRFs.

9. Deviations from the Investigational Plan

Any deviations from the study protocol will be documented as Protocol Deviations in the Source Documentation.

10. Device Accountability

The Sponsor will ship investigational devices only to the designated investigators participating in this study. The Sponsor will not ship investigational devices to any site until evidence of IRB approval has been provided to the Sponsor. All investigators are responsible for providing a secure storage location for the investigational devices, supervising device use, as well as the disposal and/or return of the devices as instructed by the Sponsor. In addition, all investigators shall maintain records to document the receipt, use and disposition of all investigational devices received by their site. The Sponsor will maintain records of all shipments and disposition of the investigational devices and will routinely inspect for device accountability at the clinical sites participating in this study.

11. Ethics

Trial Conduct

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 812).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number only. All study records will be kept in a locked research office

with limited access to study personnel and code sheets linking a patient's name to a patient identification number will be stored separately in a secured area within the research office. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

Good clinical practice (GCP) is an international quality standard that is provided by International Conference of Harmonization (ICH), an international body that defines a set of standards, which governments can then transpose into regulations for clinical trials of medications as well as medical devices involving human subjects.

GCP guidelines are important as they provide the necessary enforcement of ethics of a clinical study, protection of human rights for the subjects (such as voluntariness) and assurance of the safety and efficacy of investigational products. High standards are required in terms of comprehensive documentation for the clinical protocol, record keeping (paper and electronic which includes computers and software), training, and facilities. Quality assurance and inspections ensure that these standards are achieved and maintained.

GCP guidelines include standards on how clinical trials should be conducted, define the roles and responsibilities of clinical trial sponsors, clinical research investigators, and monitors. As a research site, we follow the ICH-GCP guidelines. Our GCP includes review of each case to determine whether or not the patient would be a good candidate for a clinical trial and if there is an appropriate clinical trial for the patient. Important aspects include adequate time for the person to review the consent form and have all questions answered, voluntarily give consent and know that they can withdraw at any time. Maintaining the subject's privacy and confidentiality is handled by assigning a subject number for each study participant. Research staff responsibilities include adherence to the protocol, proper documentation, accuracy of data and appropriate handling of the study product.

Institutional Review Board Review

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to [redacted] contact prior to the shipment of study supplies to the site. This approval must refer to the study by

exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

Any amendment to the protocol will be written by the investigator and [redacted] contact. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

Informed Consent

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25 [a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

Subjects cannot be asked to sign the Informed Consent form until the study has been fully approved by the investigational site's IRB and the Sponsor has received and reviewed the specific IRB approved Informed Consent form to be used by the site. The potential subject shall be given adequate time to read the consent form, have the study procedures explained, including risks and benefits, as well as alternative procedures, prior to signing the Informed Consent form. An example of the Informed Consent form for this study is provided in Appendix B: Informed Consent Form. The consent form must be read by the subject, the subject's questions answered, and the form signed by the subject before the treatment can be performed. All subjects are to receive copies of their signed consent form. The date the subject signs the consent form is to be recorded on CRF.

Coverage of Expenses

Subject Compensation

Subjects will not be compensated for treatment visits. They will be compensated $50 per completed followup visit.

Cost to Subjects

There will be no cost incurred by the subject for participating in this study. All noted procedures are considered standard of care (SOC) and will be billed to the patient's insurance or whatever program the patient uses.

Confidentiality

Protected health information (PHI) of clinical investigation Subjects are kept as confidential as possible in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Members of the study team who will have access to the PHI information include the following: Research staff at Joseph M. Still Research Foundation, Sponsor ([redacted]), and any outside labs/facilities that may handle specimens. When appropriate, specimens and data will only have subject ID. However, confidentiality cannot be assured.

12. Data Handling and Record Keeping

Source Documents

The investigator must maintain detailed source documents on all subjects who are enrolled or who undergo screening in the study. Source documents include subject medical records, hospital charts, clinic charts, investigator subject trial files, as well as the results of diagnostic tests (e.g., laboratory tests, hemodynamic studies).

The following minimum information should be entered into the subject's medical record:

- The date the subject entered the trial and the subject number
- The trial protocol number and the name of the Sponsor
- The date that Informed Consent was obtained
- Evidence that the subject meets the trial eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all trial related subject visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of specific device used
- Occurrence and status of any adverse events (AEs)
- The date the subject exited the trial and a notation as to whether the subject completed the trial or was discontinued, including the reason for discontinuation

Data Collection

The investigator must maintain detailed records on all subjects who sign the Informed Consent Form and begin the pre-procedure evaluation. Data for enrolled subjects will be transcribed on to CRFs provided by the Sponsor. All data should be transcribed completely, promptly and legibly. Corrections should be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one line, and initialing and dating the change, along with the reason for the change (if not obvious). Original CRF pages will be collected by the Sponsor

or Sponsor's designee after they are reviewed by the study monitor. The investigator should maintain a copy of all completed CRFs from this trial.

Trial exit forms will be completed for all enrolled subjects, regardless if they did or did not complete the trial (e.g., subject discontinuation, trial termination).

Record Retention

All records relating to the conduct of this trial are to be retained by the investigator until notified by the Sponsor or Sponsor's designee that the records may be destroyed.

13. Quality Control and Quality Assurance

Site Training

Training records shall be kept for all study-related training.

Investigator Training

Investigator Responsibilities

The investigators are responsible for ensuring that this study is conducted according to this protocol and applicable regulations and that signed Informed Consent is obtained from each subject prior to his inclusion in this study. It is the investigator's responsibility to ensure that all staff assisting with this study have the appropriate qualifications and are fully instructed on the study procedures and respect subject confidentiality, as specified in the Investigator Agreement with the Sponsor

Investigator Records

Standardized Case Report Forms (CRFs) will be used to collect complete and accurate records of the clinical data generated from this study according to Good Clinical Practices (GCP) requirements. The investigators are responsible for collecting and accurately recording the clinical data generated for this study. Investigators are also responsible for maintaining records as required by FDA per Title 21 Code of Federal Regulations (CFR) §812.140.

Investigator Reports

The investigator will be responsible for providing the following reports, in accordance with CFR§812.150, to the Sponsor for this study:

- Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs): The investigators will report by telephone, email or fax any SAEs or UADEs as soon as possible, within 24 hours of the investigator becoming aware of the event, to the Sponsor and the IRB. The Serious Adverse Event form is to be completed to document the SAE and it is to be faxed or express mailed to the Sponsor and the IRB within ten working days of the event.

- Withdrawal of Approval: If an IRB withdraws the approval to conduct this study for any reason, the investigator will notify the Sponsor as soon as possible, but in no event later than five working days after the withdrawal of the approval
- Progress Reports: The investigator will submit progress reports on the investigation to the Sponsor and the reviewing IRB at regular intervals, but in no event less often than yearly.
- Deviations from the Investigational Plan: The investigator must notify the Sponsor and the reviewing IRB of any deviation from the Investigational Plan to protect the life or physical well-being of a subject in an emergency. This notice must occur as soon as possible, but in no case longer than five working days following the occurrence of the deviation.
- Informed Consent: If the investigator uses a device without obtaining informed consent, the investigator shall report the use to the Sponsor and the IRB within 5 working days after the use occurs.
- Final Report: Within three months after the termination or completion of the study or the investigator's part in the study, the investigator shall submit a final report to the Sponsor and the IRB.
- Other Reports: Upon request from the IRB or the FDA, the investigator shall provide accurate, complete and current information about any aspect of the study.

Each investigator is responsible for ensuring that the study is conducted according to this protocol and that signed Informed Consent is obtained from each subject prior to their inclusion in this study.

14. Adverse Events and Serious Adverse Events

General

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the [redacted] contact. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the device, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and the [redacted] contact concurs with that assessment.

Adverse Event Reporting

For serious adverse events, the reporting period to [redacted] or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected. Adverse events (serious and non-serious) should be recorded on the CRF from the time

the subject has undergone one treatment through last subject visit.

Definition of an Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs or diagnosis;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of wound.

Definition of Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any AE that has any serious unfavorable and unintended sign, symptom, or disease temporally associated with the use of the devices, whether or not considered related, including those that:

- results in death
- is life-threatening
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- requires intervention to prevent permanent impairment or damage

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

Causality Assessment of Adverse Events

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the cleared medical device caused or contributed to an adverse event. If the investigator does not know whether or not medical device caused the event, then the event will be handled as "related to medical device" for reporting purposes. (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF,

as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

Adverse Event Severity Assessment

The Investigator will provide an assessment of the severity of each adverse reaction by recording a severity rating on the appropriate SAE reporting page of the subject's file. Severity, which is a description of the intensity of manifestation of the SAE, is distinct from seriousness, which implies a patient outcome or SAE-required treatment measure associated with a threat to life or functionality. Severity will be assessed according to the following scale.

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events by a member of the research staff.

Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, [redacted] is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to [redacted] must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of Exposure during pregnancy cases.

In the rare event that the investigator or member of the research team does not become aware of the occurrence of a serious adverse event immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the investigator or member of the research team is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to [redacted] in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by [redacted] to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings and/or a copy of the death certificate must be submitted as soon as possible to [redacted] or its designated representative.

All AEs/SAEs should be followed until resolution.

Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

Reporting Requirements to Regulatory Authorities

Adverse events reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

15. Committees

Data and Safety Monitoring Board

The study will be under the oversight of an independent DSMB that will assess the accumulated safety data on an ongoing basis. The role and responsibilities of the DSMB will be predefined in the DSMB charter.

16. Publication Policy

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the investigator and the [redacted] contact. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

References

1. Wolfe, R.A., et al., *Mortality differences and speed of wound closure among specialized burn care facilities.* JAMA, 1983. **250**(6): p. 763-6.
2. Burke, J.F., C.C. Bondoc, and W.C. Quinby, *Primary burn excision and immediate grafting: a method shortening illness.* J Trauma, 1974. **14**(5): p. 389-95.
3. Buinewicz, B. and B. Rosen, *Acellular cadaveric dermis (AlloDerm): a new alternative for abdominal hernia repair.* Ann Plast Surg, 2004. **52**(2): p. 188-94.
4. Kealey, G.P., et al., *Cadaver skin allografts and transmission of human cytomegalovirus to burn patients.* J Am Coll Surg, 1996. **182**(3): p. 201-5.
5. Wood, W.B., Jr., *Phagocytosis, with particular reference to encapsulated bacteria.* Bacteriol Rev, 1960. **24**(1): p. 41-9.
6. Teh, B.T., *Why do skin grafts fail?* Plast Reconstr Surg, 1979. **63**(3): p. 323-32.
7. Burleson, R. and B. Eiseman, *Mechanisms of antibacterial effect of biologic dressings.* Ann Surg, 1973. **177**(2): p. 181-6.
8. Draaijers, L.J., et al., *The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation.* Plast Reconstr Surg, 2004. **113**(7): p. 1960-5; discussion 1966-7.

17. Appendix A – NAMSA Regulatory Review Letter

400 Highway 169 South, Suite 500
Minneapolis, Minnesota, USA 55426
Office: +1-763-287-3830
Fax: +1-763-287-3836

Technical Memorandum

Date: January 11, 2019

To: Dr. Barry Markman [redacted]

From: Don F. Palme II, Ph.D., Sr Principal Product Development Strategist, Medical Research Scientist, Regulatory, NAMSA

Subject: Regulatory Review of the Tissue Texturing Process on a Variety of Materials

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Purpose

United States FDA regulatory guidance is the basis for the agency to make a determination of the safety profile of a tissue or device and the regulatory review process. This is typically assessed before a device is allowed to either enter the market (510(k)) or before a clinical study is performed (US FDA designation IDE or NDA). This regulatory review is based on safety profiles of materials and the guidance provided in law.

The purpose of this document is to provide a review of the guidance provided by the FDA with regards to the regulation of human cells tissues and cellular based products (HCT/Ps) and xenogeneic materials used for the treatment of disease.

Conclusion

Devices Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Guidance for Industry and FDA Staff (July 2007), provides: "Devices intended to process HCT/Ps *ex vivo* to create a therapeutic article, that is, products where the intended therapeutic effect is mediated by the biologic output of the device, have been assigned to CBER. For example, devices that produces autologous stem cells or hematopoietic progenitor cells for in vivo use have been assigned to CBER for review under the device provisions of the Federal Food, Drug, and Cosmetic Act (the Act), or the Public Health Service (PHS) Act. Similarly, devices that process autologous blood or tissue to produce a new HCT/P (e.g., a tissue engineered, live cell construct) at the point of care, for direct re-administration to that patient have also been assigned to CBER for review."

The tissue texturing process is performed by a device that does not produce a therapeutic effect as mediated by biological output of the device, nor does it process a new HCT/P. Thus, it does not fall under the guidance regulation and is not considered to be a medical device.

Device Description

The device is designed to create a change in the surface of a tissue in order to improve the ability of the patient to incorporate the tissue during healing. Several publications (PubMed search parameters: 12/13/2018; Search words: tissue texturing for implant which identified 24 publications of which 9 were relative to human tissue and 1 to non-human tissue) identify the benefit of tissue texturing for the improved healing response as shown by decreased capsule formation, less fibrotic tissue and decrease healing times. The device from [redacted] is capable of creating micro texturing changes in a single surface of a biological based material in a variety of patterns even on the same material (See Figures 1-3).

The texturing is performed by micro blades on the tissue and the resulting cuts [redacted] deep into the surface. This is the only changes induced by the [redacted] process on the tissue

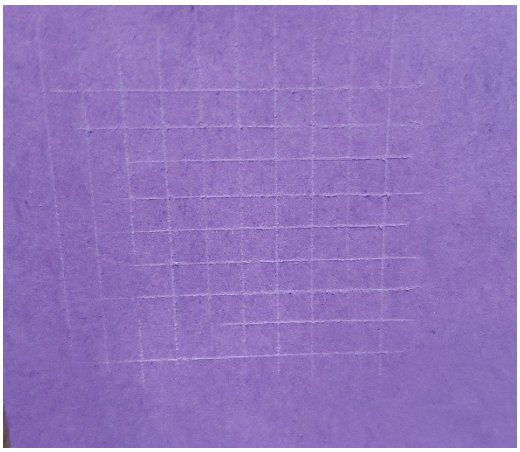

Figure 1: Amnion Textured Pattern 1

Figure 2: Amnion Textured Pattern 2

Figure 3: Dermal Textured Pattern: [redacted]

Regulatory Review

Guidance Documents Reviewed:

- Testing Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P): Specific Requirements
- Devices Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

- FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product

These guidelines direct the regulatory review process of HCT/Ps. Sections 351 and 361 of the Public Health Service Act (PHSA) provides the authority for FDA to establish regulatory requirements for marketing traditional biologics and human cells, tissues, and cellular and tissue based products (HCT/Ps). As discussed below, these two pathways differ markedly in terms of the time, effort and expense required to bring these products to market in the U.S. 21 CFR Part 1271 subpart A contains definitions and general provisions pertaining to the scope and purpose of the HCT/P regulations. Human tissue products that meet the defined criteria provided in 21 CFR Part 1271.10 are regulated solely under Section 361 of the PHSA. An HCT/P is regulated solely under Sec. 361 of the PHSA if it meets all of the following criteria:

- The HCT/P is minimally manipulated.
- The HCT/P is intended for homologous use only;
- The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage; and either:
- the HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or (ii) the HCT/P has a systemic effect
- or is dependent upon the metabolic activity of living cells for its primary function, and (a) is for autologous use; (b) is for allogeneic use in a first-degree or second-degree blood relative; or (c) is for reproductive use.

Minimal manipulation means:

1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and
2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

HCT/P's Regulated under 21 CFR 1271.3(d)(1) and Section 361 of the PHS Act by CBER

These HCT/P's are regulated solely as "361 products" when they meet all of the criteria in 21 CFR 1271.10(a):

- BONE (including DEMINERALIZED BONE)
- LIGAMENTS
- TENDONS
- FASCIA
- CARTILAGE
- OCULAR TISSUES (CORNEAS & SCLERA)
- SKIN
- VASCULAR GRAFTS (VEINS & ARTERIES), except preserved umbilical cord veins
- PERICARDIUM

- AMNIOTIC MEMBRANE (when used alone (-without added cells-) for ocular repair)
- DURA MATER
- HEART VALVE ALLOGRAFTS
- HEMATOPOIETIC STEM CELLS DERIVED FROM PERIPHERAL OR UMBILICAL CORD BLOOD
- SEMEN
- OOCYTES
- EMBRYOS

HUMAN SOMATIC CELL THERAPY AND GENE THERAPY PRODUCTS Regulated under Section 351 of the PHS Act and/or the FD&C Act. This grouping includes products that FDA has determined do not meet all of the criteria in 21 CFR 1271.10(a) and are regulated as drugs and/or biological products reviewed by CBER.

- CULTURED CARTILAGE CELLS
- CULTURED NERVE CELLS
- LYMPHOCYTE IMMUNE THERAPY
- GENE THERAPY PRODUCTS
- HUMAN CLONING
- HUMAN CELLS USED IN THERAPY INVOLVING THE TRANSFER OF GENETIC MATERIAL (cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic vector)
- UNRELATED ALLOGENEIC HEMATOPOIETIC STEM CELLS
- UNRELATED DONOR LYPHOCYTES FOR INFUSION

Materials reviewed by CDRH:

DEVICES COMPOSED OF HUMAN TISSUES Regulated under the FD&C Act and device regulations

- CORNEAL LENTICULES
- PRESERVED UMBILICAL CORD VEIN GRAFTS
- HUMAN COLLAGEN
- FEMORAL VEINS INTENDED AS A-V SHUNTS

COMBINATION PRODUCTS

- DEMINERALIZED BONE combined with HANDLING AGENTS (glycerol, sodium hyaluronate, calcium sulfate, gelatin, collagen) - are regulated as DEVICES
- BONE-SUTURE-TENDON ALLOGRAFTS - regulated as DEVICES
- CULTURED CELLS (fibroblasts/keratinocytes/nerve/ligament/bone marrow) on SYNTHETIC MEMBRANES or combined with COLLAGEN may be regulated as DEVICES or BIOLOGICAL PRODUCTS (these products are currently under review and may be regulated by CBER under either the device authorities or under section 351 of the PHS Act)

- ENCAPSULATED PANCREATIC ISLET CELLS are regulated as BIOLOGICAL PRODUCTS

[redacted] has provided the following list of tissues that can be processed using the [redacted] device:

- Human amnion/Chorion/Umbilical cord
- Human cadaveric dermal tissue – acellular
- Fetal bovine collagen
- Porcine small intestine submucosa
- Crosslinker bovine tendon collagen
- Fetal bovine dermis

Unpreserved Human Amnion/Chorion/Umbilical Cord and human cadaveric dermal tissue will be regulated under HCT/P and regulated solely under Sec. 361 of the PHSA as the materials are a HCT/P that is minimally manipulated and the [redacted] process of the HCT/P does not involve the combination of the cells or tissues with another article. Also, the textured HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function. HCT/Ps that are marketed under Section 361 are not required to obtain premarket approval/clearance from FDA. Distributors and marketers of HCT/Ps are permitted to self-designate the tissue products as meeting the criteria set forth under 21 CFR Part 1271.

If the human amnion/chorion/umbilical cord are preserved, then the material post [redacted] texturing will be reviewed by CDRH as a device using the 510(k) regulatory review.

Xenogeneic materials such as:

- Fetal bovine collagen
- Porcine small intestine submucosa
- Crosslinker bovine tendon collagen
- Fetal bovine dermis

Are in general reviewed by CDRH as a device based on the risk associated with the clinical use of the device and the nature of the materials. In general, because of the risks associated these materials they are regulated as either devices or biologics based on the source of the materials and the clinical applications. For example, INTEGRA® Artificial Skin was marketed following PMA approval.

Use of the [redacted] Surfacing Device on devices or biologics that are already marketed in the US based on the following FDA document "Is a new 510(k) required for a modification to the device? ". As stated, "A premarket notification (510(k)) is required when a legally marketed device subject to 510(k) requirements is significantly changed or modified in design, components, method of manufacture, or intended use. Significant changes or modifications are those that could significantly

affect the safety or effectiveness of the device, or major changes or modifications in the intended use of the device". Further examples provided by the FDA include:

Examples of modifications that may require a new 510(k) include, but are not limited to, the following:

- A change in indications for use from prescription use to over the counter use
- Addition of a new patient population
- Changes to the environment of use such as from professional use to home use or hospital use to ambulatory transport
- Changes in frequency or duration of use
- Change to indicate compatibility with a type of device, component, or accessory that was not indicated as compatible with the previously cleared device
- Changes in sterilization, cleaning or disinfection
- Changes in package integrity or shelf-life claims
- Changes in device design
- Changes to employ wireless communication
- Changes in the human factors of the patient or user interface
- A change in material type, formulation or chemical composition
- Changes in the antibody, detection reagents, critical reaction components or conjugates for in vitro diagnostic (IVD) devices

Based on the wording and examples provided, Use of the [redacted] Surfacing Device does not change the risk or material, formulation or chemical composition of the materials. Based on this analysis, the changes induced by the [redacted] Surfacing Device does not reach the level of change considered a major change to the device so resubmission of the device should not be required. A letter to the device file describing the change(s) and justification of regulatory position should address the regulatory requirements.

Signatures

Respectfully submitted by:

Donald F. Palme II, Ph.D.
Sr Principal Product Development Strategist, Medical Research Scientist, Regulatory, NAMSA Voting Member AATB Scientific and Technology Committee

Technical Review
Beryl St. Jeanne, Associate Regulatory Specialist, NAMSA