Title: Porcine Xenograft versus Second Intention Healing: A randomized, evaluator-blinded clinical trial

NCT Number: 03931746

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Porcine Xenograft versus Second Intention Healing: A randomized, evaluator-blinded clinical trial

Protocol Number: 18-0715

National Clinical Trial (NCT) Identified Number: 03931746

Principal Investigator: Dr. Victoria Sharon

Sponsor: Investigator Initiated

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
6.5.1	We have added a description of the "rescue therapy" that may be provided if a patient's wound has not healed at approximately 10 to 12 weeks following the surgical date. This section was previously left blank.	While typical healing time is within 12 weeks of the surgical date, it is standard of care to provide the rescue therapy at approximately 10 to 12 weeks if a patient's wound is not healing normally. Furthermore, it is not possible to assess the primary outcome (POSAS observer total score) if the wound has not healed.
9.3	We have added a sentence to this section to clarify that patients who receive the rescue therapy will be included in the Modified Intention-to-Treat Population.	We plan to analyze the data according to the treatment to which a patient was randomized. This will provide an accurate estimate of the treatment effect in the setting of actual clinical practice. Furthermore, given that typical healing time is within 12 weeks, we do not expect a large number of patients to require rescue therapy. Accordingly, the effect of the rescue therapy on treatment effect estimates would be minimal.

Table of Contents

STATEMENT OF COMPLIANCE

(1) The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

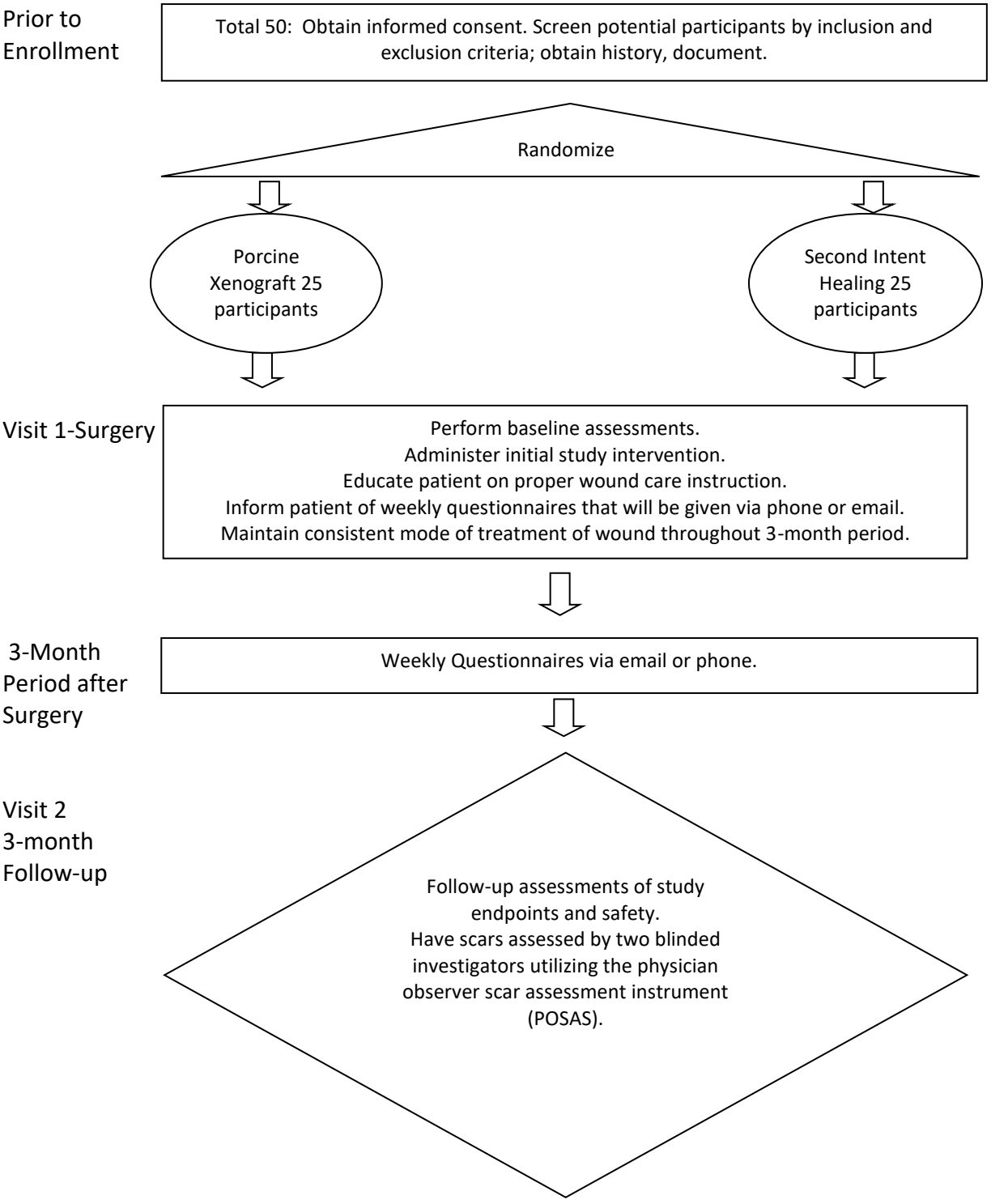
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Porcine Xenograft versus Second Intention Healing: A randomized, evaluator-blinded clinical trial
Study Description:	A comparison of porcine xenograft placement to second intent healing will be performed. Upon completion of dermatologic surgery following standard procedures, patients will be randomized into one of two groups (porcine xenograft placement or second intention healing). Weekly follow-up via questionnaires will be conducted as well as a final office visit follow-up at 3 months. Our study will allow surgeons to make informed decisions on whether porcine xenograft dressing is superior to that of second intention healing and thus worth considering.
Objectives:	Primary Objective: To compare overall scar quality and aesthetic outcome following second intention healing or porcine xenograft dressing of surgical wounds on the lower extremities. Secondary Objective: To compare patients' assessment of scar quality, healing time, scar size, pain level, and complication rates following second intention healing or porcine xenograft dressing of surgical wounds on the lower extremities.
Endpoints:	Detailed descriptions of the endpoints below are included in the body of the protocol.

	Primary Endpoint: 1. POSAS observer scale total score Secondary Endpoints: 1. POSAS patient scale total score 2. Healing time 3. Ratio of scare size to initial defect size 4. Pain score at 1 week following surgery 5. Number of weeks with pain score above 1 Safety Endpoints: 1. Infection 2. Bleeding 3. Pain
Study Population:	A total of 50 patients, over 18 years of age, post-operative defects greater than 8 mm (in greatest diameter or length of circular or oval geometric shape) on the lower extremities (including the feet) , single defect
Phase:	Device study (porcine xenograft)
Description of Sites/Facilities Enrolling Participants:	The two study sites are Dermatology Practices associated with Northwell Health. Northwell Health Physician Partners Division of Dermatology 1991 Marcus Avenue Suite 302 Lake Success, NY 11042 and 332 East Main Street Suite 1 Bay Shore, NY 11706
Description of Study Intervention:	Patients will either be randomized to receive a porcine xenograft or randomized to allow the wound to granulate via second intention.
Study Duration:	A total of 24 months.
Participant Duration:	The study participants will present to the clinic for their initial surgery and then at the 3-month (± 1 month) for wound check and photograph of the wound.

1.2 SCHEMA


Prior to Enrollment
Total 50: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Randomize
Porcine Xenograft 25 participants
Second Intent Healing 25 participants
Visit 1-Surgery
Perform baseline assessments.
Administer initial study intervention.
Educate patient on proper wound care instruction.
Inform patient of weekly questionnaires that will be given via phone or email.
Maintain consistent mode of treatment of wound throughout 3-month period.
3-Month Period after Surgery
Weekly Questionnaires via email or phone.
Visit 2 3-month Follow-up
Follow-up assessments of study endpoints and safety.
Have scars assessed by two blinded investigators utilizing the physician observer scar assessment instrument (POSAS).

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening	Enrollment/Surgery Visit 1	3-Month after surgery- Weekly Questionnaires	3 month follow-up visit ±1 month after surgery date
Informed consent	X			
Demographics	X			
Medical history	X			
Randomization	X			
Administer study intervention		X		
Physical exam (including height and weight)	X	X		X
Vital signs	X	X		X
Height	X	X		X
Weight	X	X		X
Performance status	X	X		X
Hematology				
serum chemistry [a]				
Pregnancy test [b]				
EKG (as indicated)				
Adverse event review and evaluation	X			
Complete Case Report Forms (CRFs)	X	X	X	X
Questionnaire reporting			X	
Blinded Wound/Scar Assessment				X

2 INTRODUCTION

2.1 STUDY RATIONALE

There is no clear evidence to indicate whether porcine xenograft placement is more beneficial for wound healing following dermatologic surgery (Mohs surgery or excision surgery) versus allowing the wound to heal on its own. We will perform a comparison of porcine xenograft placement to second intent healing.

2.2 BACKGROUND

Porcine xenograft has been used as a barrier to the skin for over 30 years, and due to its wound healing promoting factors, we believe that its use may result in decreased healing time, smaller scar size, better cosmetic outcomes, lower pain levels, and decreased rates of infection and other post-surgical complications.

Upon completion of dermatologic surgery following standard procedures, patients will be randomized into one of two groups (porcine xenograft placement or second intention healing). Weekly follow-up via questionnaires will be conducted as well as a final office visit follow-up at 3 months.

The application of porcine xenograft dressings for wound healing was first studied in 1985, with evidence supporting several benefits when compared to traditional dressings [1]. Subsequent studies have substantiated the use of this dressing for a variety of clinical settings [2,3].

The EZ-DERM™ porcine xenograft is a biosynthetic dressing made from porcine collagen containing aldehyde crosslinking [1,3]. It has been most commonly applied to the management of 2nd degree burns, both partial-thickness and full-thickness defects [4]. This dressing can be used for two healing purposes, either for primary healing or as an intermediate in the preparation for a skin graft [2].

Compared to other biosynthetic dressings, porcine xenografts afford longer wound adherence and can be stored at room temperature [1]. The xenograft triggers rejection by the surgical defect, increasing local vascularization [5]. It also allows for rapid granulation, a reduced risk of infection, as well as reduced wound-related fluid and thermal losses [6-8]. There is also evidence that the quicker wound healing reduces the frequency of dressings, hospitalization time, pain, and analgesic [9,10].

Several clinical case series have extended the use of porcine xenografts to Mohs Micrographic Surgery (MMS) to facilitate post-operative wound care. Porcine xenograft dressings were determined to be safe, well-tolerated, and able to be applied to a wide anatomical range [3, 11,12].

In addition to biosynthetic dressings, healing via second intention remains an alternative [13,14]. The extremities of elderly patients are a common location for wound granulation. Drawbacks to second intention healing on the extremities include prolonged healing time and extended wound care for the patient [15].

Chern et. al. completed a review of biological dressings in dermatologic surgery and concluded that there is a limited number of studies focusing on the conclusive benefits of dressings [16]. Although studies have established that EZ-DERM™ was helpful for wound healing following Mohs surgery, there have not been any definitive statistical measures reported in the literature. Additionally, there is a lack of studies assessing the direct comparison to second intention healing.

Our plan is to perform a direct comparison of porcine xenograft placement to second intent healing. Based on the previously studied benefits of the xenograft as a barrier to the skin and one which has wound healing promoting factors, we believe that its use may result in decreased healing time, smaller scar size, better cosmetic outcomes, lower pain levels, and decreased rates of infection and other post-surgical complications.

Our study will allow surgeons to make informed decisions on whether porcine xenograft dressing is superior to that of second intention healing and thus worth considering.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Second intention Healing:

Risk of infection, bleeding, scarring, numbness

Xenograft Placement:

Localized skin allergy: EZ-DERM Porcine Xenograft is latex-friendly and non-cytotoxic.
Risk of slightly longer procedure: Application of the xenograft may increase the length of the procedure by up to 10 minutes.
Risks of infection, bleeding, scarring, and numbness.
Rates of infection followed skin surgery are less than 1%.

For Both:

Risk of Randomization: Your group might receive a less effective treatment and/or have more side effects than the other treatment group(s).
Risk of loss of confidentiality: There is a possibility that documents will be seen by individuals not included in this study. However, patient data will be stored in a password-protected electronic data capture tool in order to reduce the risk of loss of confidentiality.

2.3.2 KNOWN POTENTIAL BENEFITS

There is no direct benefit to individual subjects or to the group of participants in the study

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This trial can eventually lead to porcine xenografts becoming the standard of care when it comes to wound healing.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To compare overall scar quality and aesthetic outcome following second intention healing or porcine xenograft dressing of surgical wounds on the lower extremities.	1. POSAS observer scale total score. The primary outcome will be the total score of the POSAS observer scale, assessed at the 3-month follow-up visit by two blinded evaluators who will not be involved in the placement of the porcine xenograft. For each patient, scores from the two blinded investigators will be combined by calculating the mean. The POSAS (Patient and Observer Scar Assessment Scale) is a validated assessment tool used for the	To determine whether porcine xenografts improve wound healing.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	assessment of all types of scars by professionals and patients [17-19]. The observer scale is comprised of 6 items (vascularity, pigmentation, thickness, relief, pliability, and surface area) scored on a scale from 1("like normal skin") to 10 ("worst scar imaginable"). The total score is calculated as the sum of the six items (range, 6-60). All patients will be evaluated by two blinded observers, who will be selected from the other attending physicians and/or resident physicians at the site. However, all patients will not be evaluated by the same set of observers due to differences in physician schedules. Agreement between the blinded evaluators will be assessed using the intraclass correlation coefficient (ICC). The form of the ICC will be the ICC (1,2).	
Secondary		
To compare patients' assessment of scar quality, healing time, scar size, and pain level following second intention healing or porcine xenograft dressing of surgical wounds on the lower extremities.	1. POSAS patient scale total score. Study participants will complete the POSAS patient scale at the 3-month follow-up visit. The POSAS patient scale consists of 6 items assessing patients' subjective opinion of scar quality in terms of pain, itching, color, pliability, thickness, and relief. Each item is scored from 1 (normal pigmentation, no itching, etc.) to 10 ("worst imaginable scar or sensation"). The total score of the POSAS patient scale is calculated as the sum of the six items (range, 6-60).	To determine whether porcine xenografts improve wound healing.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	2. Healing time. Healing time will be measured in weeks based on patient's responses to question 1 of the weekly follow-up questionnaire ("Is the wound completely healed (i.e., wound is completely closed with no open areas)?"). For example, a patient who first replies "Yes" to this question on the third weekly follow-up questionnaire will be assigned a healing time of 3 weeks. A more objective measure of healing time would not be feasible given our resources and patient schedule. 3. Ratio of scare size to initial defect size. The initial postoperative defect size will be measured by the investigator prior to intervention in terms of length and width using a sterile ruler. Initial defect area will be calculated as length times width. Scar size will be measured in terms of length and width at the 3-month follow-up visit, and scar area will be calculated as length times width. The outcome will be calculated by dividing the scar area by the initial defect area. 4. Pain score at 1 week following surgery. Patients' pain scores will be measured based on their response to question 2 of the weekly follow-up questionnaire. Patients will be asked to rate their current pain level at the operative site on a scale from 1 (no pain) to 10 (worst imaginable pain). 5. Number of weeks with pain score above 1. Patients' pain scores will be measured based on their response to question 2 of the weekly follow-up questionnaire. Patients will be asked	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	to rate their current pain level at the operative site on a scale from 1 (no pain) to 10 (worst imaginable pain). The POSAS observer scale, POSAS patient scale, healing time, and number of weeks with pain score above 1 are all subjective endpoints. The ratio of scar size to initial defect size and complication rates are objective endpoints.	
Tertiary/Exploratory/Safety		
To compare complication rates following second intention healing or porcine xenograft dressing of surgical wounds on the lower extremities.	1. Infection. Patient's charts will be reviewed at the completion of their 3-month office visit follow-up in order to analyze if they visited the dermatologist between the date of surgery and 3-month office visit and if infection was diagnosed. 2. Bleeding. During each of the weekly follow-up questionnaires and during the 3-month follow-up visit, patients will be asked if they have experienced any post-operative bleeding that led to a visit to the physician (yes/no) and if there was any intervention performed by the physician to stop the bleeding (yes/no). The number and percentage of patients who experienced bleeding at any time during the 3-month follow-up period will be reported.	To help keep the patients as safe as possible.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	3. Pain. The proportion of patients with a pain score > 6 at the operative site will be assessed at one week following surgery. This will be based on the patient's response to the weekly follow-up questionnaire, with scores ranging from 1 (no pain) to 10 (worst imaginable pain).	

4 STUDY DESIGN

4.1 OVERALL DESIGN

The authors will conduct a comparative two-arm study investigating outcomes of second intention healing versus porcine xenograft placement of post-operative Mohs surgery or excision wound defects. This will be a randomized evaluator blinded study with a prior power analysis. Basic demographic data will be obtained including date of birth, sex, and race. Medical record number will be retained to obtain phone number or address for patient call back should patient not show for their follow-up appointments.

Surgical defects 8 mm in diameter or larger on the lower extremities will be eligible for enrollment. Only patients with one wound will be eligible for enrollment. Primary intention (also known as linear layered) repair is not feasible in many patients with defects on the foot, ankle, or distal extremity as these are sites under high tension and poor circulation. Patients with small post-op defects many also opt not to be sutured via primary intention to avoid physical activity restrictions due to the increased risk of wound dehiscence. When closed via primary intention, a 0.8cm defect results in a scar of greater than or equal to 2.4cm.

Patients will be randomly assigned in a 1:1 ratio to receive either a porcine xenograft or to allow the wound to granulate via second intention. If primary/linear repair is not an acceptable option, the standard of care at Northwell is to allow the wound to heal on its own via second intention post-operatively. Due to recently published retrospective studies, there is a suggestion that porcine xenografts may be a feasible alternative to second intent healing. Currently, it is the surgeon's (and patient's) choice, after a discussion of risks and benefits of each modality, what is done.

A randomization schedule will be generated by the Biostatistics Unit at the Feinstein Institute for Medical Research to assign a repair method (porcine xenograft placement or second intention healing).

Block randomization will be used to ensure balance in the number of patients allocated to each treatment group. The randomization schedule will be uploaded to REDCap by a statistician outside of the study team. The PI, who will screen eligible subjects, will not have user rights for the Randomization Setup module within REDCap, and will thus be blinded to which treatment arm is next on the randomization list. Due to the nature of the treatment, it will not be possible to blind the patients. Patients will be asked not to inform the blinded physician observers which treatment they received. The PI will use the "Randomize" button within REDCap to assign patients to porcine xenograft or second intention healing after they have been consented and enrolled in the study.

Prior to intervention the defect size will be measured in terms of length and width using a sterile ruler.

After procedure completion wound care instruction will include daily dressing changes and application of petroleum jelly using a cotton tipped applicator to the wound daily until it is healed.

Weekly questionnaires will be given to the patients by phone or email follow-up. All complications and adverse events would be monitored and recorded for both study groups. Assessment of the scar will be blinded in nature.

The mode of treatment for participants will remain consistent throughout the 3-month period, as both methods are reliable for this type of defect. It is not general practice to place a xenograft on a wound healing by second intention or to remove a xenograft after one has been placed to switch to second intention. Should there be any complications, a modified intention to treat principle, described in Section 9, will be adhered to.

The scars for both study groups will be measured at a single follow up visit after 3 months ± 1 month, and two blinded investigators will then assess the scar for the primary efficacy endpoint at this time. The blinded evaluators will be other MDs not involved in the study who are working in the dermatology department. The Principle Investigator will speak with the physician to outline what needs to be recorded for each patient. The validated physician observer scar assessment instrument (POSAS) will be used for this purpose. Scar size will consist of a length x width measurement using a ruler.

The research team consists of one physician who will perform all of the surgical procedures, which will remove bias in technique. The study statistician will be blinded to the treatment groups in order to avoid bias or the appearance of bias. The statistician will keep the information on which treatment is "A" and which treatment is "B".

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

To compare overall scar quality, aesthetic outcome, healing time, scar size, pain level, and complication rates following second intention healing or porcine xenograft dressing of surgical wounds on the lower extremities.

4.3 JUSTIFICATION FOR DOSE

This is a device study not a drug trial.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

- Over 18 years of age
- Able to give informed consent themselves
- Willing to return for follow-up visits
- Post-operative defects greater than 8 mm (in greatest diameter or length of circular or oval geometric shape) on the lower extremities (including the feet)
- Single defect

5.1 EXCLUSION CRITERIA

- Mentally handicapped
- Unable to understand written and oral English
- Incarceration
- Under 18 years of age
- Unwilling to return for follow-up
- Pregnant women
- Wounds less than 8 mm in length
- Wounds on the head, neck or digits
- Patients in which primary linear closure is recommended

5.2 LIFESTYLE CONSIDERATIONS

During this study, participants will discuss with the physician any limitations of activities based on the treatment provided, as is done with the normal protocol.

5.3 SCREEN FAILURES

Patients will either qualify to receive the device or don't.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients scheduled for cutaneous surgery at the Northwell Health Dermatology Clinics at Lake Success and Bay Shore will be approached by the research staff to see if they are interested in participating in the study. A pre-operative surgical consultation for lower extremity cutaneous malignancies is not standard of care. As such, many dermatologic surgery patients receive same-day consult and surgery. Thus it is, in the majority of cases, not feasible to obtain consent prior to the day of surgery. It would pose a burden on the patient and surgeon and may result in delay of surgical care to require a pre-operative surgical consultation prior to treatment of lower extremity cutaneous malignancies.

Patients will not be encouraged nor coerced in any way. We do not plan to advertise this study, as the patient population in the department will produce sufficient opportunities to identify patients. Subjects are not compensated for participation in this study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Only patients with one wound will be eligible for enrollment. Primary intention (also known as linear layered) repair is not feasible in many patients with defects on the foot, ankle, or distal extremity as these are sites under high tension and poor circulation. Patients with small post-op defects many also opt not to be sutured via primary intention to avoid physical activity restrictions due to the increased risk of wound dehiscence. When closed via primary intention, a 0.8cm defect results in a scar of greater than or equal to 2.4cm.

Patients will be randomized to either receive a porcine xenograft or allow the wound to granulate via second intention. If primary/linear repair is not an acceptable option, the standard of care at Northwell is to allow the wound to heal on its own via second intention post-operatively. Due to recently published retrospective studies, there is a suggestion that porcine xenografts may be a feasible alternative to second intent healing. Currently, it is the surgeon's (and patient's) choice, after a discussion of risks and benefits of each modality, what is done.

Prior to intervention the defect size will be measured in terms of length and width using a sterile ruler.

After procedure completion wound care instruction will include daily dressing changes and application of petroleum jelly using a cotton tipped applicator to the wound daily until it is healed.

6.1.2 DOSING AND ADMINISTRATION

There will be no dosing since patients will either be randomized to receive the porcine xenograft or continue with second intent healing.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Normal porcine xenograft procedures that the dermatology practice follows.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Normal porcine xenograft procedures that the dermatology practice follows.

6.2.3 PRODUCT STORAGE AND STABILITY

Normal porcine xenograft procedures that the dermatology practice follows.

6.2.4 PREPARATION

Normal porcine xenograft procedures that the dermatology practice follows.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

A randomization schedule will be generated by the Biostatistics Unit at the Feinstein Institute for Medical Research to assign a repair method (porcine xenograft placement or second intention healing). Block randomization will be used to ensure balance in the number of patients allocated to each treatment group. The allocation ratio will be 1:1. The randomization schedule will be uploaded to REDCap by a statistician outside of the study team. The PI, who will screen eligible subjects, will not have user rights for the Randomization Setup module within REDCap, and will thus be blinded to which treatment arm is next on the randomization list. The PI will use the "Randomize" button within REDCap to assign patients to porcine xenograft or second intention healing as they are enrolled.

There will be one physician who will perform all of the surgical procedures, which will remove bias in technique. There will additionally be two blinded physicians who will be tasked with observing the scar and assessing the primary efficacy endpoint (POSAS observer scale total score). The study statistician will be blinded to the treatment groups in order to avoid bias or the appearance of bias. All data provided to the statistician will list the treatment group as "A" or "B".

6.4 STUDY INTERVENTION COMPLIANCE

Porcine xenograft placement and second intention healing are methods of healing that are currently used and is the patient's and physician's choice. Administration of either porcine xenograft or second intention is part of the standard of care and will be completed as such. An initial visit form will be completed to log the method of treatment administered and will be reviewed to ensure that the randomized treatment was completed.

6.5 CONCOMITANT THERAPY

For this protocol no prescription medication will be utilized as this is a device study.

6.5.1 RESCUE MEDICINE

The study sites will supply the topical application of rescue medication that will be obtained locally. The following rescue medications may be used:
Silver Nitrate Wood Applicator Sticks
Henry Schein Model: 1126994

The use of rescue medication is allowable after the formation of hypergranulation tissue which may begin to occur 6-8 weeks post-operatively, but typically the use of rescue medications should be delayed, if possible, for at least 10-12 weeks following the surgical date. This is considered standard of care, as it allows the patient the chance to heal without adjunct medication. The date and time of rescue medication administration as well as the name and regimen of the rescue medication will be recorded in RedCAP. Follow-up after the application of the rescue medication will occur every 6 weeks or until healed, per our surgical standard of care.

For patients receiving rescue medication, the POSAS observer scale total score (primary outcome), POSAS patient scale total score (secondary outcome), and ratio of scar size to initial defect size (secondary outcome) will be recorded at the patient's follow-up visit within 6 weeks of administering the rescue medication, or at a subsequent follow-up visit when the wound is fully healed. (Note that it is not possible to administer the POSAS instrument, a scar assessment tool, if the wound is not completely healed).

As described in Section 9.3, a modified intention-to-treat analysis will be used, in which all patients who have been assessed for the primary study endpoint will be analyzed according to their randomized treatment group.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from porcine xenograft placement does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation
- Specific complications
- Scar size
- Pain score

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

If patients decide to withdraw from the study, there is no danger involved with early withdrawal. Patients will be advised to follow up with the surgeon as normal standard of care outside the research setting.

Should patients wish to have their porcine xenograft removed following enrollment in the porcine xenograft arm or suffer from other complications resulting in porcine xenograft failure, they will be assessed in an intention to treat method.

7.3 LOST TO FOLLOW-UP

If patients fail to show up for the follow-up visit, they will be withdrawn from the study. An evaluable patient will be one who completes the final 3 month follow -up office visit.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The authors will conduct a comparative two-arm study investigating outcomes of second intention healing versus porcine xenograft placement of post-operative Mohs surgery or excision wound defects.

This will be a randomized evaluator blinded study with a prior power analysis. Basic demographic data will be obtained including date of birth, sex, and race. Medical record number will be retained to obtain phone number or address for patient call back should patient not show for their follow-up appointments.

Surgical defects 8 mm in diameter or larger on the lower extremities will be eligible for enrollment. Only patients with one wound will be eligible for enrollment. Primary intention (also known as linear layered) repair is not feasible in many patients with defects on the foot, ankle, or distal extremity as these are sites under high tension and poor circulation. Patients with small post-op defects many also opt not to be sutured via primary intention to avoid physical activity restrictions due to the increased risk of wound dehiscence. When closed via primary intention, a 0.8cm defect results in a scar of greater than or equal to 2.4cm.

Patients will be randomized to either receive a porcine xenograft or allow the wound to granulate via second intention. If primary/linear repair is not an acceptable option, the standard of care at Northwell is to allow the wound to heal on its own via second intention post-operatively. Due to recently published retrospective studies, there is a suggestion that porcine xenografts may be a feasible alternative to second intent healing. Currently, it is the surgeon's (and patient's) choice, after a discussion of risks and benefits of each modality, what is done.

Prior to intervention the defect size will be measured in terms of length and width using a sterile ruler.

After procedure completion wound care instruction will include daily dressing changes and application of petroleum jelly using a cotton tipped applicator to the wound daily until it is healed.

Weekly questionnaires will be given to the patients by phone or email follow-up until 12 weeks post-surgery.

The mode of treatment for participants will remain consistent throughout the 3-month period, as both methods are reliable for this type of defect. It is not general practice to place a xenograft on a wound healing by second intention or to remove a xenograft after one has been placed to switch to second intention. Should there be any complications, a modified intention to treat principle, described in Section 9, will be adhered to.

The scars for both study groups will be measured at a single follow up visit after 3 months ± 1 month, and two blinded investigators will then assess the scar at this time. The blinded evaluators will be other MDs not involved in the study who are working in the dermatology department. The Principle Investigator will speak with the physician to outline what needs to be recorded for each patient. The validated physician observer scar assessment instrument (POSAS) will be used for this purpose. Scar size will consist of a length x width measurement using a ruler.

The research team consists of one physician who will perform all of the surgical procedures, which will remove bias in technique.>

8.2 SAFETY AND OTHER ASSESSMENTS

Each patient will undergo examination of the surgical defect. Any adverse effects will be recorded. Formal safety endpoints are described in Section 9.4.4. Standard protocol for porcine xenograft placement and secondary intention will be followed.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Adverse events (AE) or suspected adverse reactions in dermatologic surgery are associated with postoperative hemorrhage and hematoma formation, graft necrosis, flap necrosis, postoperative infection, and wound dehiscence. However, the rate of complications is low at 1.6%. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Dr. Victoria Sharon, MD will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Dr. Victoria Sharon will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Events will be documented accordingly and reported to Northwell Health's IRB.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This definition could include an 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 device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1))

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- **Primary Efficacy Endpoint(s):** The primary efficacy endpoint is the **POSAS observer scale total score**, evaluated at the 3-month follow-up visit (detailed in Section 9.4.2). The Mann-Whitney U test will be used to assess the superiority of porcine xenograft to second intention healing with respect to this endpoint. A two-sided hypothesis test will be used.

  H_0: The distributions of POSAS observer scale total score are equal for patients treated with porcine xenograft and second intention healing.
  H_1: The distributions of POSAS observer scale total score are not equal for patients treated with porcine xenograft and second intention healing.

- **Secondary Efficacy Endpoint(s):** The Mann Whitney U test will be used to assess the superiority of porcine xenograft to second intention healing for each of the secondary endpoints below. Additional details for each endpoint are provided in Section 9.4.3. Two-sided hypothesis tests will be used.

1. **POSAS patient scale total score**, evaluated at the 3-month follow-up visit by study participants.
2. **Healing time**, measured in weeks based on patient's responses to question 1 of the weekly follow-up questionnaire.
3. **Ratio of scare size to initial defect size**
4. **Pain score at 1 week following surgery**
5. **Number of weeks with pain score above 1**

9.2 SAMPLE SIZE DETERMINATION

A total of 50 patients (25 per group) will be recruited in order to ensure adequate power to compare groups on the primary efficacy endpoint, POSAS observer scale total score. Based on a two-sample t-test, a total sample size of 38 will provide 80% power to detect a significant difference between groups, assuming a true difference of 6 points, pooled standard deviation of 6.5 [20], and an alpha level of .05. Given that the asymptotic relative efficiency (ARE) of the Mann-Whitney U test relative to the two-sample t-test is no less than 0.864 [21], regardless of the underlying distribution, a sample size of 44 (38/0.864) will achieve equal power. In order to account for 10% attrition, we will recruit a total of 50 patients.

The assumed difference of 6 points was based on the PI's clinical judgment of the minimal clinically important difference for the POSAS observer scale, which ranges from 6 to 60. It was also informed by previous research which considered 6 points the minimal clinically important difference when comparing second intention healing to an alternative closure method. [20] The mean POSAS observer score among patients treated with second intention healing was estimated at 19.9 in this prior study. Based on this estimate, an improvement of 6 points or more would correspond to a mean POSAS score of 13.9 or lower for patients treated with porcine xenograft.

9.3 POPULATIONS FOR ANALYSES

A modified intention to treat analysis will be performed. All patients will be analyzed according to randomized treatment assignment, unless a patient prefers an alternative treatment method between the time he/she is randomized and the procedure (in which case the patient will be excluded from the study). The **Modified Intention-to-Treat (mITT) Population** will consist of all patients who receive the study intervention and show up for the 3-month office visit follow-up, during which the primary endpoint is evaluated. The Modified Intention-to Treat Population will also include patients who required the rescue therapy, and had the primary endpoint assessed at a follow-up visit when the wound had completely healed. This population will be used to analyze the primary endpoint and all secondary endpoints.

The **Safety Population** will consist of all patients who receive the randomized study intervention. This population will be used to analyze all safety endpoints.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics will be produced to summarize the demographic and clinical characteristics of the two study arms. For continuous variables, means and standard deviations (SD) will be provided, as well as medians and interquartile ranges (IQR). For categorical variables, frequencies and percentages will be provided.

All hypothesis tests will be two-sided, and evaluated at the .05 level of significance. 95% confidence intervals will be provided for inferential tests. Statistical analysis will be performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

1. **POSAS observer scale total score.** The primary efficacy endpoint will be the total score of the POSAS observer scale, assessed at the 3-month follow-up visit by two blinded evaluators who will not be involved in the placement of the porcine xenograft. For each patient, scores from the two blinded investigators will be combined by calculating the mean. The POSAS (Patient and Observer Scar Assessment Scale) is a validated assessment tool used for the assessment of all types of scars by professionals and patients [17-19]. The observer scale is comprised of 6 items (vascularity, pigmentation, thickness, relief, pliability, and surface area) scored on a scale from 1("like normal skin") to 10 ("worst scar imaginable"). The total score is calculated as the sum of the six items (range, 6-60). This is a subjective endpoint, given that it is based on the evaluating physician's judgment of each scale item.

All patients will be evaluated by two blinded observers, who will be selected from the other attending physicians and/or resident physicians at the site. However, all patients will not be evaluated by the same set of observers due to differences in physician schedules. Agreement between the blinded evaluators will be assessed using the intraclass correlation coefficient (ICC). The form of the ICC will be the ICC(1,2).

Statistical Analysis: The Mann Whitney U test will be used to compare the two study arms on the primary efficacy endpoint based on the mITT Population defined in Section 9.3. No adjustments for multiplicity will be made because there is only one primary endpoint, and this endpoint will not be evaluated during the planned interim safety analysis.

We will summarize the POSAS observer scale score for the two study arms using the mean (SD), and median (IQR). As a measure of effect size between the porcine xenograft and second intention healing groups, we will calculate the Hodges-Lehmann estimate of the median difference, and corresponding 95% confidence interval. This is equal to the median of all paired differences between observations in the porcine xenograft and second intention healing groups.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Analysis of all secondary endpoints will be considered exploratory. Thus, the analysis of secondary endpoints is not dependent on findings of the primary endpoint, and no adjustments for multiplicity will be made.

1. **POSAS patient scale total score.** Study participants will complete the POSAS patient scale at the 3-month follow-up visit. The POSAS patient scale consists of 6 items assessing patients' subjective opinion of scar quality in terms of pain, itching, color, pliability, thickness, and relief. Each item is scored from 1 (normal pigmentation, no itching, etc.) to 10 ("worst imaginable scar or sensation"). The total score of the POSAS patient scale is calculated as the sum of the six items (range, 6-60).

2. **Healing time.** Healing time will be measured in weeks based on patient's responses to question 1 of the weekly follow-up questionnaire ("Is the wound completely healed (i.e., wound is completely closed with no open areas)?"). For example, a patient who first replies "Yes" to this question on the third weekly follow-up questionnaire will be assigned a healing time of 3 weeks. A more objective measure of healing time would not be feasible given our resources and patient schedule.

3. **Ratio of scare size to initial defect size**. The initial postoperative defect size will be measured by the investigator prior to intervention in terms of length and width using a sterile ruler. Initial defect area will be calculated as length times width. Scar size will be measured in terms of length and width at the 3-month follow-up visit, and scar area will be calculated as length times width. The outcome will be calculated by dividing the scar area by the initial defect area.

4. **Pain score at 1 week following surgery.** Patients' pain scores will be measured based on their response to question 2 of the weekly follow-up questionnaire. Patients will be asked to rate their current pain level at the operative site on a scale from 1 (no pain) to 10 (worst imaginable pain).

5. **Number of weeks with pain score above 1.** Patients' pain scores will be measured based on their response to question 2 of the weekly follow-up questionnaire. Patients will be asked to rate their current pain level at the operative site on a scale from 1 (no pain) to 10 (worst imaginable pain).

The POSAS patient scale, healing time, and number of weeks with pain score above 1 are all subjective endpoints. The ratio of scar size to initial defect size is an objective endpoints.

Statistical Analysis: The Mann Whitney U test will be used to compare the two study arms on each of the secondary endpoints based on the mITT Population defined in Section 9.3.

We will summarize each secondary endpoint for the two study arms using the mean (SD), and median (IQR). As a measure of effect size between the porcine xenograft and second intention healing groups, we will calculate the Hodges-Lehmann estimate of the median difference, and corresponding 95% confidence interval. This is equal to the median of all paired differences between observations in the porcine xenograft and second intention healing groups.

9.4.4 SAFETY ANALYSES

Safety Endpoints:

1. **Infection.** Patient's charts will be reviewed at the completion of their 3-month office visit follow-up in order to analyze if they visited the dermatologist between the date of surgery and 3-month office visit and if infection was diagnosed.

2. **Bleeding**. During each of the weekly follow-up questionnaires and during the 3-month follow-up visit, patients will be asked if they have experienced any post-operative bleeding that led to a visit to the physician (yes/no) and if there was any intervention performed by the physician to stop the bleeding (yes/no). Bleeding will be considered an adverse event if an intervention by a physician was required to stop the bleeding. The number and percentage of patients who experienced bleeding at any time during the 3-month follow-up period will be reported.

3. **Pain**. The proportion of patients with a pain score $\geq$ 6 at the operative site will be assessed at one week following surgery. This will be based on the patient's response to the weekly follow-up questionnaire, with scores ranging from 1 (no pain) to 10 (worst imaginable pain).

Statistical Analysis: We will report the frequency and proportion of patients experiencing each of the safety endpoints above, based on the Safety Population defined in Section 9.3.The proportion of patients experiencing each type of complication (infection, bleeding, pain) will be compared between porcine xenograft and second intention healing using Fisher's exact test.

In addition to the planned safety analysis at the completion of the study, one interim analysis will be conducted by the study statistician after 26 patients have been randomized and complete the final study visit at 3 months post-intervention. This is equal to approximately 50% of the planned enrollment goal of 50 patients. The purpose of this interim analysis will be to review the safety endpoints. There will be no formal stopping rule based on the statistical significance of the interim safety analysis. The principal investigator will alert the IRB immediately if there is any evidence or suggestion of a difference between treatment groups with regard to AEs or SAEs. Additional details on this interim safety analysis are included in Section 9.4.6.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline demographic and clinical characteristics will be provided for the two study arms. Continuous variables will include age and initial post-op defect size (length x width, cm^2). Categorical variables will include sex, race, ethnicity, procedure type (Mohs, Excisions), surgical site, current tobacco use, use of other antibiotics at time of surgery, use of topical or systemic prophylaxis after surgery, and past medical history of: blood thinners, immunosuppresants, diabetes, venous stasis, and skin infection. Past medical history will be self-reported by the patient.

Continuous variables will be summarized using means (SD) and medians (IQR). Categorical variables will be summarized using frequencies and percentages. Significance tests will not be used for baseline comparisons.

9.4.6 PLANNED INTERIM ANALYSES

One interim analysis will be conducted after 26 patients have been randomized and complete the final study visit at 3 months post-intervention. This is equal to approximately 50% of the planned enrollment goal of 50 patients. The purpose of this interim analysis will be to review the safety endpoints delineated in Section 9.4.4. The primary efficacy endpoint (Observer POSAS score) and all secondary endpoints will not be evaluated. Thus, the interim analysis will not impact the Type I error rate for the primary efficacy analysis.

The number and proportion of patients who experience each of the adverse events below will be summarized, and compared between study arms using Fisher's exact test. Definitions and assessment procedures for these endpoints have been described in Section 9.4.4.

- Infection
- Bleeding
- Pain score at the operative site > 6 at week 1 post-intervention

The number and proportion of patients who experience any serious adverse event (SAE), as defined in Section 8.3.2, will be summarized and compared between study arms using Fisher's exact test. Given the minimal risk associated with dermatologic surgery, we do not anticipate any serious adverse events [22].

The interim safety analysis will be performed by Andrew Strunk, the study statistician. The statistician will be blinded to the treatment groups. All data provided to the statistician will list the treatment group as "A" or "B". The results of the interim safety analysis will be presented to the Principal Investigator, Dr. Victoria Sharon, who will be unblinded to the groups corresponding to "A" and "B".

There will be no formal stopping rule based on the statistical significance of the interim safety analysis. The principal investigator will alert the IRB immediately if there is any evidence or suggestion of a difference between treatment groups with regard to AEs or SAEs.

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol, ICF. Participants will also be asked to sign the Northwell A/V recording authorization for permission to photograph their wounds.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the 1991 Marcus Avenue Suite 302 Lake Success, NY 11042 Dermatology Practice and 332 East Main Street Suite 1 Bay Shore, NY 11706 Dermatology Practice. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by 1991 Marcus Avenue Suite 302 Lake Success, NY 11042 Dermatology Practice and 332 East Main Street Suite 1 Bay Shore, NY 11706 Dermatology Practice research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the 1991 Marcus Avenue Suite 302 Lake Success, NY 11042 Dermatology Practice and 332 East Main Street Suite 1 Bay Shore, NY 11706 Dermatology Practice.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the 1991 Marcus Avenue Suite 302 Lake Success, NY 11042 Dermatology Practice. Data will be stored electronically via REDCap.

Biological samples will not be obtained in this study.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Victoria Sharon, MD, Director of Dermatologic Surgery &	N/A

Dermato-Oncology and Attending Physician, Department of Dermatology	
Northwell Health Physician Partners Division of Dermatology	
1991 Marcus Avenue Suite 302 Lake Success, NY 11042	
(516) 719-3376	
vsharon@northwell.edu	

10.1.6 SAFETY OVERSIGHT

Safety oversight will be conducted by the study team during the planned interim analysis. Safety data will be assessed for each arm of the study as described in Section 9.4.6.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by Dr. Victoria Sharon and Joshua Burshstein, a research assistant who is part of the study team.
- Dr. Sharon is the physician performing the surgery and applying the method of healing. Dr. Sharon will monitor the clinical safety of the patients via analysis of the follow-up data.
- Monitoring activities will focus on the following processes: informed consent process, timely completion of eCRF forms, participant follow-up, review of data entry, and missing data.
- An initial monitoring assessment will be conducted after the fifth patient has been enrolled, and subsequent assessments will be completed after approximately every 20 patients have been enrolled.
- During monitoring assessments, the study team will
    - Verify that appropriate signatures and dates were obtained for consent documents for all participants.
    - Review 100% of data contributing to the primary endpoint.
    - Review documentation of adverse events and reporting of serious adverse events

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.]

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

All study documents will be retained as part of standard patient protocol as the participants are patients of the practice as well. There is no sponsor for this study.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, and reported to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the <specify NIH Institute or Center (IC)> has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest>

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure

UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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