A Single Arm, Single Center Pilot Study Evaluating the Safety and Healing Time of a Decellularized, Whole Donor Nipple-Areola Complex Reconstruction Graft

Study Protocol and Statistical Analysis Plan

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A Single Arm, Single Center Pilot Study Evaluating the Safety and Healing Time of the NACgraft™ for Nipple-Areolar Complex Reconstruction

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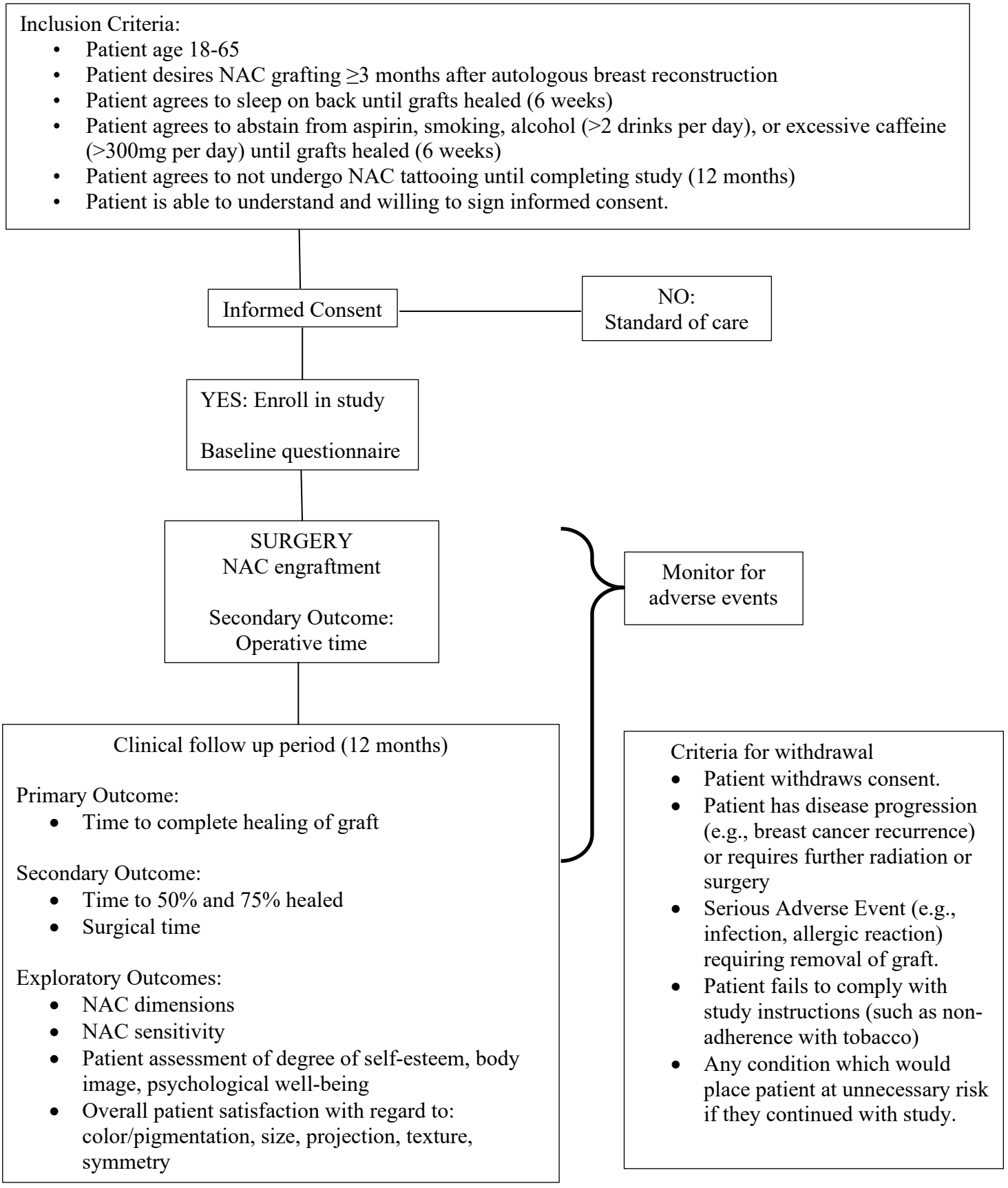
PROTOCOL SYNOPSIS

TITLE	A Single Arm, Single Center Pilot Study Evaluating the Safety and Healing Time of the NACgraft™ for Nipple-Areolar Complex Reconstruction
STUDY PHASE	Feasibility
INDICATION	Nipple-Areola Complex (NAC) Reconstruction
INVESTIGATIONAL PRODUCT OR PROCEDURE	NACgraft™ - a decellularized skin allograft of the human nipple-areolar complex
PRIMARY OBJECTIVE(S)	To evaluate safety and healing time after NAC reconstruction with the BioAesthetics' NACgraft™.
SECONDARY OBJECTIVE(S)	To evaluate operative time, NAC vascularization, dimensions, sensation, and patient satisfaction up to 12 months after reconstruction surgery with the BioAesthetics' NACgraft™.
TREATMENT SUMMARY	This single arm pilot study is designed to obtain preliminary safety, healing, patient satisfaction and other data in adult female subjects undergoing uni- or bilateral nipple-areola complex reconstruction with the BioAesthetics' NACgraft™. The study consists of a screening period (up to 3 weeks before engraftment) to determine study eligibility and prepare the NACgraft(s)™, a treatment period during which time uni- or bilateral engraftment surgery is performed, and a follow-up period during which time safety, healing time, vascularization, nipple dimensions and sensitivity, and patient satisfaction are assessed. The total duration of the study is approximately 13 months for each subject. Up to 20 female subjects will be screened in order to perform NAC engraftment on 15 subjects. Primary, secondary and exploratory endpoints will be assessed up to 12 months after engraftment. On the day of surgery, NACgrafts™ will be engrafted according to standard reconstructive technique. Using sterile technique, the recipient site on the breast mound will be de-epithelialized sharply and meticulous hemostasis obtained with electrocautery. The NACgraft™ will then be sutured into place. In women undergoing bilateral NAC reconstruction, this process will be repeated for the contralateral breast. A sterile dressing will be applied and patients will be discharged home according to institutional guidelines; written

	instructions will be provided for the care of the NACgraft(s)™ and dressings. The dressing will include antimicrobial ointment, followed by a non-adherent, occlusive dressing (e.g. Adaptic, Xeroform) secured in place using a foam dressing cut into a donut (e.g., Allevyn) to prevent compression of the graft. Patients will be return to the outpatient clinic regularly until the graft(s) are fully healed: on or about postoperative Days 7, 14, 28, and 42. They will return on days 90, 180, and 360 for measurement of long-term endpoints including nipple dimensions, sensitivity, and for satisfaction survey completion.
SAMPLE SIZE	N=15 patients
STATISTICAL CONSIDERATIONS	Time to complete healing for each NAC will be defined as the first weekly visit at which the graft has been deemed to be >99% epithelialized. Max, Mean, Median, and 95% Confidence Interval of these data will be presented, as will percent (%) healed over time for each graft. No formal statistical testing will be performed for any other endpoint; summary statistics will be presented at each time point.

SCHEMA


Inclusion Criteria:
• Patient age 18-65
• Patient desires NAC grafting ≥3 months after autologous breast reconstruction
• Patient agrees to sleep on back until grafts healed (6 weeks)
• Patient agrees to abstain from aspirin, smoking, alcohol (>2 drinks per day), or excessive caffeine (>300mg per day) until grafts healed (6 weeks)
• Patient agrees to not undergo NAC tattooing until completing study (12 months)
• Patient is able to understand and willing to sign informed consent.
Informed Consent
NO:
Standard of care
YES: Enroll in study
Baseline questionnaire
SURGERY
NAC engraftment
Secondary Outcome:
Operative time
Monitor for adverse events
Clinical follow up period (12 months)
Primary Outcome:
• Time to complete healing of graft
Secondary Outcome:
• Time to 50% and 75% healed
• Surgical time
Exploratory Outcomes:
• NAC dimensions
• NAC sensitivity
• Patient assessment of degree of self-esteem, body image, psychological well-being
• Overall patient satisfaction with regard to: color/pigmentation, size, projection, texture, symmetry
Criteria for withdrawal
• Patient withdraws consent.
• Patient has disease progression (e.g., breast cancer recurrence) or requires further radiation or surgery
• Serious Adverse Event (e.g., infection, allergic reaction) requiring removal of graft.
• Patient fails to comply with study instructions (such as non-adherence with tobacco)
• Any condition which would place patient at unnecessary risk if they continued with study.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
BD-NRC	Biodesign® Nipple Reconstruction Cylinder
BMSC	Bone Marrow-Derived Mesenchymal Stem Cell
BMI	Body mass index
CGTP	Current Good Tissue Practices
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
Dcl-NHP-NAC	Decellularized Non-Human Primate Nipple-Areolar Complex
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ECM	Extracellular Matrix
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCT/P	Human Cells, Tissues, and Cellular and Tissue-Based Products
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IDE	Investigational Device Exemption
IRB	Institutional Review Board
NAC	Nipple-areolar complex
NACgraft™	Decellularized human nipple-areolar complex graft
NHP	Non-Human Primate
N-NAC	Native Nipple-Areolar Complex
PD	Protocol Director
SAE	Serious Adverse Events
SRC	Scientific Review Committee
SWM	Semmes Weinstein Monofilament
VAS	Visual Analog Scale

1. OBJECTIVES

1.1. Primary Objective

To evaluate safety and healing time after nipple-areola complex reconstruction with the BioAesthetics' NACgraft™.

1.2. Secondary Objectives

To evaluate operative time, NAC vascularity, dimensions (projection, sensitivity), sensitivity, and patient satisfaction up to 12 months after nipple-areola complex reconstruction surgery with the BioAesthetics' NACgraft™.

2. BACKGROUND

2.1. Study Disease

There are over 3.5 million breast cancer survivors in the US, many of whom have undergone reconstructive surgery.[1] Close to one-third of early stage and two-thirds of late-stage breast cancer patients opt for mastectomies.[1,2] Patients without a NAC continue to experience psychological distress even after the breast mound has been reconstructed.[3] NAC reconstruction is of key psychological importance for these patients, decreasing feelings of distress and increasing body image and self-esteem.[4,5] Women with NAC reconstruction have significantly higher sexual well-being, aesthetic and general satisfaction, and quality of life scores, as compared to women without NAC reconstruction.[6,7] However, there is no standard, viable method to reliably reconstruct a permanent and natural NAC. Current NAC reconstruction options are limited to rubber prostheses, 3D tattoos, and surgical techniques to create NAC-like structures from a patient's own skin tissue or acellular dermal allografts.[8–10] These approaches produce NACs that either lack physical depth or fail to maintain a protrusion for more than a few months.[11,12] According to breast reconstructive surgeons, current methods of nipple reconstruction are the limiting factor for a complete breast reconstruction.

2.2. Study Device

The BioAesthetics NACgraft™ is a decellularized NAC derived from deceased human donors. Proprietary washing/rinsing steps provide a removal of immunologic elements (including cells and nucleic acids). The NACgraft™ is then packaged in a tube containing sterile PBS for individual attachment to a de-epithelialized portion of the human breast after breast reconstruction and is protected with dressings until re-vascularization, re-epithelialization and dermal/neural elements repopulate the device, leaving a living human NAC substitute. By preserving the ECM of the native human NAC, including its non-immunogenic signaling molecules and structural format, the BioAesthetics NACgraft™ serves as a scaffold that allows vascular, neural, dermal and epithelial infiltration until the time of complete healing. The BioAesthetics NACgraft™ has been studied extensively in *in vitro* and in preclinical models including mice and non-human primates to demonstrate their safety and therapeutic potential, as detailed in **Section 2.5**.[21,22]

BioAesthetics' NACgraft™ fits within the Food and Drug Administration (FDA)'s HCT/P (Human Cells, Tissues, and Cellular and Tissue-Based Products (21 CFR Part 1271)) regulatory pathway (see Appendix A1 of Investigator's Brochure). To advance to clinical use, the product is manufactured in accordance with Current Good Tissue Practices (CGTP) and must submit a registration with the FDA 90 days prior to marketing. The NACgraft™ will be registered with the FDA prior to study initiation. Therefore, no Investigational Device Exemption (IDE) is required for this feasibility study.

2.3. Rationale

Over 200,000 mastectomies are performed annually in the US for the prevention or treatment of breast cancer.[1] These surgeries involve the partial or complete removal of the breast tissue, including the NAC. Additionally, more than 3.5 million breast cancer survivors are living in the US, many of whom have had mastectomies.[1] Close to one-third of early stage and two-thirds of late stage breast cancer patients opt for mastectomy as a treatment.[1,2] Following mastectomy, over 70% of women elect to undergo reconstruction.[13] NAC reconstruction can have a significant impact on a woman's psychological well-being.[14–16] Women are more comfortable undergoing a mastectomy if the nipple can be spared during the procedure, or if nipple reconstruction is possible when nipple-sparing is not an option.[17] Research has shown that the NAC may play a more significant role in determining psychological well-being than the reconstructed breast mound. NAC reconstruction has been shown to correlate with self-esteem and improved body image. Furthermore, NAC reconstruction provides a sense of closure to their cancer experience.[4,5] Close to 80% of women who underwent NAC reconstruction would describe NAC reconstruction as being important and would encourage other women to undergo NAC reconstruction.[6] Women with NAC reconstruction are described feeling more confident in social settings, more emotionally capable, emotionally healthy, self-confident, feminine, attractive, and "normal".[6] Women with NAC reconstruction have higher sexual well- being, general and aesthetic satisfaction, and quality of life scores compared to women without NAC reconstruction.[6,7]

Despite the widespread popularity and health benefits of post-mastectomy NAC reconstruction, current options for reconstruction are often inadequate. Options for NAC reconstruction include three-dimensional (3D) tattooing, adhesive prosthetics, acellular collagen matrix derived from porcine intestinal submucosa, or surgical techniques to create NAC-like structures from skin tissue such as local flaps or nipple-sharing grafts, or acellular dermal matrix sheets.[8–10] Unfortunately, these approaches either lack physical depth or fail to maintain a 3D structure for more than a few months.[11,12] Patient outcomes for surgical NAC reconstruction are dependent on surgical skill and time, and patients often end up requiring additional costly revisions when their reconstruction NAC(s) lose projection. Furthermore, nipple-sharing grafts are not feasible for all patients and only available for women who have had a unilateral mastectomy and have a nipple of adequate size.[18] Use of decellularized porcine small intestinal submucosa, such as Cook Medical's Biodesign® Nipple Reconstruction Cylinder (BD-NRC) has had mixed results, retaining only an average of 40% nipple projection at 12 months post reconstruction.[12] Thus, there remains a great need for an easy-to-apply, permanent, and aesthetically pleasing method for NAC reconstruction.

These clinical challenges inspired the BioAesthetics group to develop the NACgraft™, which serves as a scaffold for NAC regeneration that can be engrafted onto the exterior of the body on a de-epithelialized wound bed (onlay engraftment) in the anatomical location of the NAC. The NACgraft™ onlay graft differs from previous acellular allografts, which are intended for subcutaneous placement. This graft undergoes a patent-pending decellularization process which has been rigorously developed, characterized, and published in peer-reviewed journals.[19,20]

2.4. Study Design

This **single arm** pilot study is designed to obtain preliminary safety and performance data in adult female subjects following **treatment** with the BioAesthetics' NACgraft™. NACgrafts will be surgically engrafted onto 15 patients, via uni- or bilateral onlay engraftment. Given the nature of the treatment, this is an **open** (no masking) trial. **No randomization** will occur. The primary outcome being evaluated is **safety/efficacy** of the treatment approach. The overall study design is as follows:

- Potential patients will be screened to determine study eligibility up to 3 weeks before the engraftment.
- On the day of surgery, NACgrafts will be engrafted according to standard reconstructive technique. Using sterile technique, the recipient site on the breast mound will be de-epithelialized sharply and meticulous hemostasis obtained with electrocautery. The NACgraft™ will then be sutured into the wound bed with dissolving suture. In women undergoing bilateral NAC reconstruction, this process will be repeated for the contralateral breast. A sterile dressing will be applied and patients will be discharged home according to institutional guidelines; written instructions will be provided for the care of the NACgraft(s) and dressings. The dressing will include antimicrobial ointment, followed by a non-adherent, occlusive dressing (e.g. Adaptic, Xeroform) secured in place using a foam dressing cut into a donut (e.g., Allevyn) to prevent compression of the graft.
- Safety, healing time, sensation, vascularization, patient satisfaction, and nipple characteristics will be assessed over a 12-month period. Patients will return to the outpatient clinic on postoperative Days 7, 14, 28, and 42. Visits thereafter will take place on days 90, 180, and 360 post-engraftment.

2.5. Correlative Studies Background

The BioAesthetics NACgraft™ has been studied extensively in *in vitro* and in preclinical models to demonstrate their safety and therapeutic potential, as detailed below.[21,22]

In a recent study,[21] NAC tissue was harvested from rhesus macaques according to institutional guidelines and decellularized through a modified protocol.[23,24] Briefly, NAC grafts are incubated with a series of agents alternating with water including Triton X-100, sodium deoxycholate, sodium chloride, antibiotic/antimycotic agents, and DNase I, then stored in antibiotic/antimycotic solution until use. This process removes cellular components while preserving the extracellular matrix (ECM) structure. Decellularized NACs were subjected to histological and quantitative analyses, including culture with bone marrow-derived mesenchymal stem cells (BMSCs) *in vitro*. They were found to be completely devoid of cells while retaining ECM integrity and a high degree of bioactivity. Specifically, collagen and glycosaminoglycan content were not significantly altered by decellularization, whereas elastin content was significantly decreased. The graft promoted BMSC proliferation and viability *in vitro*.

In a follow up study, nonhuman primate (NHP)-derived NAC tissue was decellularized and their ECM components analyzed by both proteomic and histological analyses.[22] Decellularized NHP NAC grafts again showed the removal of intact cells and a greatly diminished intracellular protein profile, as compared with intact NHP NAC tissue. Decellularized NAC grafts were then tested in a murine model. N=15 mice received subcutaneous implantation of a decellularized-NHP-

NAC (dcl-NHP-NAC group 1 and 2). Additional groups included native NAC (N-NAC), commercial control (Strattice, catalog No. 1016002; LifeCell Corporation, Branchburg, NJ), or surgery only (sham). Two dcl-NHP-NAC groups were included to reflect different decellularization batches. Tissue was harvested at days 2, 14, 21. Histology revealed greater neovascularization in dcl-NHP-NAC grafts as compared to the commercial control, with no observed biocompatibility issues. The grafts were then tested in an NHP model. Briefly, 18 dcl-NHP-NACs and two native host nipples were onlay grafted onto partial thickness wounds along the dorsal midline of resus macaques. Grafts were harvested at weeks 1, 3, and 6 for histological analysis. Results demonstrated successful neovascularization of the grafts that reached a steady state by 3 weeks post-engraftment. Furthermore, grafts showed complete re-epithelialization by 3 weeks, which remained unchanged through the end of the study.

This approach has now been replicated using human-derived NAC grafts implanted in an NHP model (manuscript in preparation). Results showed graft re-epithelialization, vascularization, and the presence of nerves within graft tissue by the 6-week timepoint, with preserved nipple projection. In summary, the above preclinical trials confirm the safety and clinical potential for this device to improve patient care.

2.6 **Nipple Morphology and Pigmentation Considerations**

When a NAC is recovered from a deceased donor, the areola diameter, nipple diameter, and nipple projection/height are measured. These characteristics and pertinent demographic information (age, race, BMI, etc.) will be tracked with each NAC as part of inventory. For consistency in the manufacturing process, the diameters of the areolas are uniformly sized to 2 cm, but the diameters (usually < 2 cm) and projections of the nipples themselves are not altered. We will categorize the NACgrafts as small, medium, and large on the basis of both nipple diameter and projection. In speaking with patients, it is clear that each has a unique preference for nipple size. When the physician places an order, the size preference will be matched from the inventory.

With respect to pigmentation, the process of decellularization generally removes all pigment (melanin) from the graft such that it appears as a pale white color just like Alloderm® or other acellular dermis products. In individuals with very darkly pigmented NACs, we sometimes see that a layer of melanin remains on the surface of the NACgraft after decellularization. In our studies of NACgraft engraftments on non-human primates whose skin lacks melanin, we saw that after healing occurred (6 weeks) the color of regenerated NAC was the same as the surrounding skin tissue, but with a pink hue due to blood vessel infiltration. On a microscopic level, what we saw is that cells infiltrated the graft and lined up along the basement membrane between the epidermis and dermis of the NACgraft and regenerated a new epidermis underneath the existing decellularized epidermis, sloughing off the decellularized epidermis. So, from these observations, we expect that regardless if melanin (only contained in the epidermis) remains on the surface of the graft or not after decellularization, it will be sloughed off during the healing process and the graft will take on the color of the patient's surrounding skin. Therefore, we expect that NACgrafts do not need to matched for race. Since non-human primates do not have melanin, we could not ascertain from those studies whether the NACgrafts promote higher concentrations of melanocytes/melanin than normal skin and, therefore, result in a darker

pigmented NAC as compared to surrounding skin. If a patient is not satisfied with the color of their new NAC, tattooing can be performed after healing is complete.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1. Inclusion Criteria

3.1.1. Women between 18 and 65 years old. No race-ethnic restrictions.

3.1.2. Patient has undergone uni- or bi-lateral autologous breast reconstruction a minimum of 3 months prior to enrolling in the study.

3.1.3. Patient agrees to sleep on her back until the graft(s) have healed (approximately 6 weeks).

3.1.4. Patient agrees to abstain from taking aspirin, drinking alcohol (>2 drinks per day), or consuming excessive amounts of caffeine (>300mg per day) until the graft(s) have healed (approximately 6 weeks).

3.1.5. Patient agrees to not undergo NAC tattooing until completing the study (approximately 12 months after engraftment).

3.1.6. Patient is able to understand and willing to sign an informed consent form.

3.1.7. Eastern Cooperative Oncology Group (ECOG) or Karnofsky Performance Status restrictions: N/A

3.1.8. Life expectancy restrictions: N/A

3.1.9. Requirements for organ and marrow function: N/A

3.2. Exclusion Criteria

3.2.1. Patient is currently smoking or using tobacco or nicotine products (i.e. patch, gum, or nasal spray) or has used such products in the past 12 months.

3.2.2. Patient has a history of delayed wound healing, Vitamin C deficiency, diabetes (Type I or Type II), BMI<18.5 or >40 kg/m, or any other uncontrolled comorbidity.

3.2.3. Patient is currently receiving radiation or chemotherapy or received radiation to the breast wall.

3.2.4. Patient has a history of prior NAC reconstruction

3.2.5. Patient has had NAC tattooing.

3.2.6. Therapy restrictions: none

3.2.7. Investigational Agent restrictions: none

3.2.8. Patient has a history of allergic reaction to any decellularized biologic matrix product.

3.2.9. No patient will be excluded from the study due to history of HIV or cancer.

3.3. Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4. Randomization Procedures

No randomization will occur.

3.5. Study Timeline

Primary Completion:

The study will reach primary completion 24 months from the time the study opens to accrual.

Study Completion:

The study will reach study completion 24 months from the time the study opens to accrual.

4. TREATMENT PLAN

On the day of surgery, NACgrafts™ will be engrafted according to standard reconstructive technique. Using sterile technique, the recipient site on the breast mound will be de-epithelialized sharply and meticulous hemostasis obtained with electrocautery. The NACgraft™ will then be sutured into the wound bed with dissolving suture (e.g., chromic gut). In women undergoing bilateral NAC reconstruction, this process will be repeated for the contralateral breast. A sterile dressing will be applied, and patients will be discharged home according to institutional guidelines; written instructions will be provided for the care of the NACgraft(s)™ and dressings. The dressing will include antimicrobial ointment, followed by a non-adherent, occlusive dressing (e.g. Adaptic, Xeroform) secured in place using a foam dressing cut into a donut (e.g., Allevyn) to prevent compression of the graft.

Patients will be return to the outpatient clinic regularly until the graft(s) are fully healed: on or about postoperative Days 7, 14, 28, and 42. They will return on days 90, 180, and 360 for measurement of long-term endpoints including nipple dimensions, sensitivity, and for satisfaction survey completion.

In the event that the NAC Graft fails, the surgeon will determine if re-grafting is appropriate. The patient will be offered to undergo a second NAC Graft procedure.

4.1. General Concomitant Medication and Supportive Care Guidelines

Patients will continue their regular medications and receive routine postoperative following NAC reconstruction. No additional supportive medications are needed. No use of radioisotopes or radiation machines are required for the study. The procedures performed are similar to normal postoperative care following NAC reconstruction. The risks associated with the intervention are the same risks as with other surgical NAC reconstruction techniques, and include allergic reaction, asymmetry, swelling, graft failure requiring revision/debridement, hematoma, infection requiring debridement and/or antibiotics, scarring, delayed healing, and unsatisfactory aesthetic results.

4.2. Criteria for Removal from Study

Reasons for patient withdrawal from the study include the following:

- Patient withdraws consent.
- Patient has disease progression (e.g., breast cancer recurrence on the side(s) of NAC reconstruction), requiring additional treatment such as surgery or chemotherapy.
- Unacceptable adverse events, such as infection, hematoma, or allergic reaction requiring removal of the NACgraft.
- The patient fails to comply with the study guidelines or postoperative care instructions (such as non-adherence with tobacco)
- Any other medical condition which would place the patient at unnecessary risk if they were to continue in the study, determined on a case-by-case basis.

4.3. Alternatives

There will be several tiers of risk protection implemented in the proposed clinical study.

- Risk Protection by Graft Manufacturing: The first tier of risk protection for the proposed study is in the manufacturing of BioAesthetics' NACgrafts™. Grafts will be decellularized and manufactured according to current Good Tissue Practices (CGTP) guidelines. See Investigator's Brochure and Instructions for Use.
- Risk Protection by Subject Selection Criteria: The first clinical risk mitigation strategy is to conduct a thorough subject eligibility screening according to our explicitly defined, carefully reviewed study inclusion/exclusion criteria. In addition to representing the patient characteristics defining our anticipated indications for use, these eligibility criteria ensure the selection of subjects who have an acceptably low-risk profile, and for whom participating in our study does not present a significant elevation of risk. These criteria will be identified during the recruitment process and through a review of the user's medical history. In addition, patients with characteristics that may elevate their risk of infection or injury as part of the current study will be excluded:
  - Tobacco usage
  - Delayed wound healing
  - Vitamin C deficiency
  - Diabetes
  - Uncontrolled comorbidity
  - Body mass index outside of 18.5-29.9 kg/m^2 range
  - Currently receiving radiation or chemotherapy, or have received radiation to breast wall

Note - these individuals will be allowed to enroll if their conditions can be resolved prior to study enrollment. We will also carefully confirm that all enrolled subjects exhibit sufficient cognitive capacities, maximizing their ability to respond appropriately in the event of any complications – e.g., by contacting study personnel.

- Risk Protection by HIPAA Compliance: Potential loss of patient privacy and confidential information is possible but is expected to be a low risk as institutional and federal HIPAA regulations will be followed to protect patient data. The clinical site will operate according to standard HIPAA-compliant procedures for handling of routine clinical data, and all research data will be entered/uploaded directly to the secure clinical study validation software on a daily basis. Hard copies of any research-specific data collection forms will be kept in a secure, locked file cabinet, to which only the clinical site's lead investigator and study coordinator will have access as designated in the final study protocol. All members of the clinical staff participating in the study will maintain strict HIPAA compliance, and the results gathered will be treated as confidential, thus requiring all staff to maintain confidentiality to minimize risk to privacy. By using standard, validated procedures and best practices for handling clinical research data wherever possible and tailoring these processes to the standard procedures and workflow of Stanford Hospital & Clinics to the extent possible, the likelihood of success will be maximized and the possibility of data breach will be minimized.
- Specific clinical study measures to manage risk will focus on routine subject monitoring in the form of weekly and monthly clinical visits. These will be conducted by a study nurse or coordinator, and include visual inspection, performed by at least one surgeon, for complications and extent of healing. During the clinical visits, patients will be prompted to answer a brief verbal survey to screen for any adverse events. Patient satisfaction will also be assessed at 6 and 12 months. If subjects exhibit symptoms indicative of adverse events requiring medical attention, which are defined by a detailed clinical decision tree, she will receive medical attention as necessary and appropriate.
- Incidental findings arising from study data will be discussed between the clinical site lead investigator and BioAesthetics' team, at regularly scheduled data review meetings.

There are no applicable alternate procedures or treatments. Any patients who exit before engraftment will not receive a NACgraft for nipple replacement. However, these patients may opt to undergo nipple reconstruction – with BioAesthetics' NACgraft™ or a commercial alternative – at a later time point. Any patients who exit after engraftment will have had nipple reconstruction and the benefits and risks associated with the NACgraft™. Current commercial alternatives include:

- Surgical techniques that create a NAC-like structure from existing local or secondary tissues or acellular dermal matrix sheets, such as Alloderm or Glyaderm
- 3D tattooing

- Cook Medical's Biodesign Nipple Reconstruction Cylinder® (BD-NRC), an acellular collagen matrix derived from porcine intestinal submucosa. BD-NRC plugs still requires the same local or secondary site nipple reconstruction.

5. INVESTIGATIONAL DEVICE INFORMATION

5.1. Investigational Device

See NACgraft™ Investigator's Brochure for complete investigational device information.

5.2. Intervention Description

This is a single-arm interventional study. The study group will undergo NAC reconstruction in the office or operating room depending on any concurrent procedures. Following antiseptics and injection of local anesthesia, an area of skin on the reconstructed breast mound is de-epithelialized with a scalpel. After obtaining hemostasis with bovie electrocautery, the graft is sewn in place using an absorbable suture. A soft dressing is then placed over the graft (antibiotic ointment, non-adherent occlusive dressing, foam/sponge dressing cut into a donut). The dressing is taken down on postoperative day 7 at the patient's first follow up appointment. Dressings are continued until epithelialization is complete over the entire graft (this is anticipated to occur over 4-6 weeks). The Foam dressings will be used for 6 weeks to prevent graft compression.

5.3. Availability

BioAesthetics Corporation will provide the NACgrafts™.

5.4. Agent Ordering

BioAesthetics will be notified upon patient enrollment and NACgrafts™ will be prepared and shipped to study site up to 3 weeks prior to engraftment.

Grafts will be sent to the Hagey Laboratory for Pediatric Regenerative Medicine at Stanford:

257 Campus Dr. West, GK 200
Stanford, CA 94305
Phone: 650.736.2776

The NACgrafts™ will be stored according to BioAesthetics' defined protocol prior to surgery.

5.4. Agent Accountability

The NACgrafts™ will be kept in a secure storage location, accessible only to study personnel, to avoid access to unauthorized persons.

6. DOSE MODIFICATIONS

Due to the nature of the device, does modifications are not relevant to this study.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1. Potential Adverse Events

The potential risks have been identified below. The existing standard of care would be applied to any adverse event. More detailed risk mitigation strategies are described in section **4.3 – Alternatives.**

Loss of Privacy and Confidentiality: Potential loss of patient privacy and confidential information is possible.

Medical Risks: The potential risks will be summarized in the consent form and will be reviewed with the patient by the surgeon or study coordinator (as designated in the final protocol). Patients will additionally be able to access a member of the study team with any questions pertaining to risks for this study.

Since a surgical procedure is required for the placement of the BioAesthetics NACgraft™, there are several expected adverse events that are related to the surgery itself. These are similar to the risks with any nipple reconstruction procedure and they include:

- Swelling/edema
- Infection
- Wound contracture
- Pain
- Bleeding
- Lack of or abnormal sensation
- Unanticipated cosmetic result
- Asymmetry
- Scarring
- Need for revisionary procedures

Adverse events that may result from the use of NACgraft™ itself include, but are not limited to the following:

- Lack of device integration
- Lack of device epithelialization
- Device slough
- Abnormal coloration with healing
- Allergic reaction to remaining trace amounts of processing reagents listed in the Cautions section.
- Graft rejection
- Transmission of known pathogens including Hepatitis B or C, HIV I/II, syphilis or other bacteria.
- Transmission or causation of diseases of unknown etiology and characteristics.

7.2. Adverse Event Reporting

Adverse events will be graded according to CTCAE v4.03. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 days after the study

treatment.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

8. CORRELATIVE/SPECIAL STUDIES

No further correlative laboratory or animal studies are planned.

9. STUDY CALENDAR

	Screening	Day 0	Day 7[a]	Day 14[a]	Day 28[a]	Day 42[a]	Day 90[a]	Day 180[a]	Day 360[a]	Personnel	Description
Informed Consent	X									Study Site Staff	
Height and Weight (for BMI)	X									Study Site Staff	
Medical History	X									Study Site Staff	
Vital Signs	X	X	X	X	X	X	X	X	X	Study Site Staff	Patient vital signs (heart rate, blood pressure, temperature) will be taken with the patient in a seated position and medications will be recorded.
Current Medications	X	X	X	X	X	X	X	X	X	Study Site Staff	
NACgraft Engraftment		X								Surgeon	
Surgical Time		X								Study Site Staff	Duration will be the time difference between initial incision of the wound bed (i.e. de-epithelialization) and placement of the final suture.
Discontinue Nipple Protector						X				Surgeon	The use of nipple protector bandage will be discontinued after 6 weeks[b].
Photographs[a]	X	X	X	X	X	X	X	X	X	Study Site Staff	Digital photographs of each NACgraft will be taken for documentation and transmission to surgeon for specified endpoints.
Wound Healing			X	X	X	X	X	X	X	Surgeon	Visual inspection of the graft(s) will be conducted to assess the extent of NACgraft healing and identify any complications (e.g. necrosis, infection). Assessments will be performed by the study site Surgeon and, using the photographs. Wound healing will be assessed via the following metrics: epithelialization (0-100%), granulation (0-100%), ischemia/necrosis (0-100%), dehiscence (0-100%), and overall healing (0-100%).
Infection			X	X	X	X	X	X	X	Surgeon	Grafts will be assessed for infection via the following metrics: A) no infection; B) hyperemia (no infection); C) cellulitis (superficial infection); D) abscess or purulent infection.
Vascularity					X	X	X	X	X	Surgeon +	An assessment of blood flow to the NAC will be determined visually both by the surgeon and, using the digital photographs, by surgeon.. The NAC color will be graded as white, pink, light brown, blue, purple or black. In addition, each NACgraft will be pricked with a lancet/lancing device (the type used for obtaining fingerstick glucose measurement) in each quadrant of the areola, plus the nipple, for a total of 5 regions to determine vascularization. Lancing will be discontinued after the first post-operative visit demonstrating vascularity.
Graft Dimensions						X	X	X	X	Study Site Staff	Nipple projection/height and diameter will be measured with a Depth Gauge and Drill Gauge, respectively.
NAC Sensitivity	X						X	X	X	Surgeon	Sensitivity testing will be performed with the patient laying down and eyes closed. The areola will be divided into 4 quadrants, plus the nipple, for a total of 5 regions to be tested using the Semmes Weinstein monofilament technique.
Patient Surveys	X						X	X	X	Study Site Staff	Patients will complete the Nipple Reconstruction Satisfaction Survey – Pre at Screening and Nipple Reconstruction Satisfaction Survey – Post at Days 90, 180, and 360.
a: window +/- 4 days| b: subject discretion and/or PI discretion to continue beyond 6 weeks											

10. MEASUREMENTS

10.1. Primary outcome measure: time to complete healing

10.1.1. Relevant Subset

All patients (n=15).

10.1.2. Measurement Definition

Time to healing for each NACgraft will be as the first weekly visit at which the surgeon deems the graft >99% overall healed. This measurement will be reported as the number of weeks to healing.

10.1.3. Measurement Methods

Degree of healing will be based on visual assessment by the surgeon with the following metrics on a visual analog scale (VAS): vascularization, overall healing (0-100%). Photographs will be taken, stored and transmitted securely to BOX. Time to complete healing will be defined as the first visit at which the surgeon determine that there is >99% overall healing of the graft.

10.1.4. Measurement Time Points

Healing assessment will take place at each postoperative visit until healed including day 7, 14, 28, and 42. Further early postop follow up visits may be considered as determined by the surgeon.

10.1.5. Response Review

N/A

10.2. Primary outcome measure: device safety

10.2.1. Relevant Subset

All patients (n=15).

10.2.2. Measurement Definition

Safety of the device will be measured by any observed complications that occur following treatment. Primary safety endpoints will include presence/absence of infection, necrosis, allergic reaction, or any complication that can be attributed to the graft procedure. The degree and frequency of these adverse events will be recorded and reported. These endpoints will be reported in the study case report form (CRF) and will be continuously tabulated and reviewed by the study staff.

10.2.3. Measurement Methods

Photographs will be taken using standardized digital photography, stored and transmitted securely to surgeon for independent review. Grafts will be evaluated by the surgeon with the following metrics on a visual analog scale (VAS): ischemia/necrosis (0-100%); dehiscence (0-100%). In evaluating for complications, the surgeon will classify grafts as having A) no infection; B) hyperemia (no infection); C) cellulitis (superficial infection); D) abscess or purulent infection. Additional adverse events or complications (as defined in CTCAE v4.03, see **Section 7.2**) will also be recorded and reported in categorical format.

10.2.4. Measurement Time Points

Healing assessment will take place at each postoperative visit until healed including day 7, 14, 28, and 42. Further early postop follow up visits may be considered as determined by the surgeon.

10.2.5. Response Review

N/A

10.3. Secondary outcome measure: Time to 50% and 75% graft healing

10.3.1. Relevant Subset

All patients (n=15).

10.3.2. Measurement Definition

Time to 50% and 75% healing for each NACgraft™ will be as the first weekly visit at which the surgeon deems the graft >50% healed and >75% healed, respectively. This measurement will be reported as the number of weeks to healing.

10.3.3. Measurement Methods

See **Section 10.1.3.**

10.3.4. Measurement Time Points

See **Section 10.1.4.**

10.3.5. Response Review

See **Section 10.1.5.**

10.4. Secondary outcome measure: operative time

10.4.1. Relevant Subset

All patients (n=15).

10.4.2. Measurement Definition

Operative time will be defined as the amount of time passing between incision of the skin and final suture placement during graft surgery.

10.4.3. Measurement Methods

Operative time will be measured in the procedure room with a standard stopwatch and reported in minutes/seconds. If in the operating room this is reported by operating staff. If done in the clinic, the procedural nurse will assist with timekeeping. Operative time will be recorded separately for each NACgraft™ during bilateral procedures.

10.4.4. Measurement Time Points

Measurements will take place on day 0 (day of surgery)

10.4.5. Response Review

N/A

10.5. Secondary outcome measure: NAC sensitivity

10.5.1. Relevant Subset

All patients (n=15).

10.5.2. Measurement Definition

NAC sensitivity is defined as the sensation felt by the patient on the NACgraft™ according to the scale in **Section 10.5.3.**

10.5.3. Measurement Methods

Measurement is performed using Semmes Weinstein Monofilament (SWM) testing with the patient lying down with her eyes closed. The areola will be divided into quadrants, so a total of 5 regions (nipple + each areolar quadrant) will be assessed. Each monofilament represents a log of the force needed to bend the microfilament, with the larger monofilaments requiring more force to bend. Filament sizes will be converted to categorical variables (0 = no sensation, i.e. unable to feel 6.65 filament; 1 = can feel 6.65 filament, 2 = can feel 4.56 filament, 3 = can feel 4.31 filament, 4 = can feel 3.61 filament, and 5 = can feel 2.83 filament).

10.5.4. Measurement Time Points

Measurements will take at 3 months, 6 months, and 12 months.

10.5.5. Response Review

N/A

10.6. Secondary outcome measure: Nipple projection

10.6.1. Relevant Subset

All patients (n=15).

10.6.2. Measurement Definition

Nipple projection is defined as the distance from the breast mound to the most projecting tip of the NACgraft, reported in millimeters.

10.6.3. Measurement Methods

Nipple projection is measured with the patient laying down on her back using a depth gauge

10.6.4. Measurement Time Points

Measurements will take place on day 0 (day of surgery), day 42, 3 months, 6 months, and 12 months.

10.6.5. Response Review

N/A

10.7. Secondary outcome measure: Nipple diameter

10.7.1. Relevant Subset

All patients (n=15).

10.7.2. Measurement Definition

Nipple diameter is defined as the diameter of the nipple at its base (i.e. where it sits on the breast mound), reported in centimeters.

10.7.3. Measurement Methods

Nipple diameter is measured using a drill gauge.

10.7.4. Measurement Time Points

Measurements will take place on day 0 (day of surgery), day 42, 3 months, 6 months, and 12 months.

10.7.5. Response Review

N/A

10.8. Secondary outcome measure: patient satisfaction

10.8.1. Relevant Subset

All patients (n=15).

10.8.2. Measurement Definition

Patient satisfaction will be measured using a standardized postoperative survey utilizing a LIKERT (numerical) scale to collect feedback from the patient on a variety of indicators including NAC position, overall appearance, symmetry, color, softness, sensation, appearance while nude, appearance when clothed, size, projection, and effect on overall breast appearance. Feedback will additionally be obtained in regard to contribution of reconstructed NAC on sex life, well-being, self-esteem, and whether the patient would undergo the procedure again or recommend the procedure to others. Scores will be reported on a scale of 1 (strongly disagree) to 5 (strongly agree).

A pre-operative survey will collect feedback from the patient on their perceived satisfaction with their reconstructed breast prior to NAC reconstruction. Survey items include satisfaction with breast shape, sensation, sense of well-being, self-esteem, and sex life.

10.8.3. Measurement Methods

Patient satisfaction pre- and post-NAC reconstruction will be measured using standardized Pre-Operative and Post-Operative Nipple Reconstruction Satisfaction Surveys (see Appendix B).

10.8.4. Measurement Time Points

The time point will take place at study enrollment (pre-operative survey) and postoperatively at 3 months, 6 months, and 12 months.

10.8.5. Response Review

N/A

10.9. Secondary outcome measure: NAC vascularization

10.9.1. Relevant Subset

All patients (n=15).

10.9.2. Measurement Definition

NAC vascularization is defined by the presence of vascular tissue within the graft. Presence of bleeding from the graft following needle puncture using a lancet device will serve as the objective confirmation of vascularization.

Visual assessment using categories on a color chart (white, pink, light brown, blue, purple or black) will also be performed.

10.9.3. Measurement Methods

Presence of bleeding will be determined using a lancet device after cleaning the area with an alcohol swab. Results are reported for 5 quadrants (four corners plus central nipple). Once a quadrant shows bleeding, lancing is deferred for all future visits.

Visual assessment using categories on a color chart (white, pink, light brown, blue, purple or black) will be performed at all follow up visits specified in **Section 10.9.4**.

10.9.4. Measurement Time Points

Measurements will take place on day 28, 42, 3 months, 6 months, and 12 months.

10.9.5. Response Review

N/A

11. REGULATORY CONSIDERATIONS

11.1. Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2. Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3. Data Management Plan

The Protocol Director, or his designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will

be developed using the REDCap database system and will be maintained by the Study Coordinator. CRFs will be kept in a locked office, only accessible to the research team.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

The purpose of this clinical study is to determine the initial safety and utility of BioAesthetics' NACgraft™. The proposed sample size of 15 subjects is not intended to support definitive conclusions around our primary outcome measures, but rather to:

- Provide support that the NAC graft is safe for marketing purposes
- Confirm ability to gather necessary data for an adequately powered larger clinical study in the future
- Provide preliminary estimates of these measures and their associated variability, in part to better define sample size requirements for a future larger study.

Outcome measures for this study address:

- Safety: For safety, we are collecting data on the degree of healing and the incidence of engraftment- related adverse events (e.g. infection, necrosis).
- Performance: For graft performance, we are collecting data on the following:
    - Degree and timing of healing
    - Duration of surgical engraftment procedure
    - Nipple characteristics
        - Projection
        - Sensitivity
        - Vascularization
- Patient Satisfaction: Finally, we will access user experience from satisfaction surveys addressing the following areas:
    - Body image
    - Overall satisfaction
    - Satisfaction with nipple
    - Self-esteem
    - Psychological well-being

Additionally, we will assess the completeness of feasibility study data in terms of missing or incomplete measurements for each outcome and will determine any associated operational modifications needed to enhance data collection in a future study. Preliminary estimates will be developed for each type of measure. Each estimate will be assessed with descriptive statistics (t distribution for continuous variables, Poisson distribution for incidence rates, etc.) and 95% confidence intervals will be applied.

12.1.1. Randomization

No randomization will take place.

12.2. Interim analyses

No statistical stopping rule will be employed.

12.3. Descriptive Statistics and Exploratory Data Analysis

Descriptive statistics will be employed including t distribution for continuous variables, Poisson distribution for incidence rates, etc. and 95% confidence intervals will be applied for the measured primary and secondary outcomes.

12.4. Primary Analysis

Primary outcome measure: To evaluate safety and healing rates following NAC reconstruction using the BioAesthetics NACgraft™.

12.4.1. Analysis Population

All study participants will be included in the analysis population. Intention-to-treat analysis will be performed and statistics for sub-groups containing no missing data or non-adherence will be included.

12.4.2. Analysis Plan

Time to complete healing for each NAC will be defined (as described in **Section 10.1**) as the first weekly visit at which the surgeon deems the graft >99% overall healed. This outcome will be characterized in terms of distributional characteristics such as the maximum, mean, median, and variation (as 95% confidence interval) of these data.

Safety outcome data as described in **Section 10.2** that are reported as percentages (ischemia/necrosis, erythema, dehiscence) will be characterized in terms of distributional characteristics such as the maximum, mean, median, and variation (as 95% confidence interval). Measurements reported as categorical variables (infection) will be characterized as a percent.

12.5. Secondary Analysis

Secondary outcome measures include time to 50% and 75% healing, operative time, nipple projection, nipple diameter, NAC sensitivity, NAC vascularization, and patient satisfaction survey scores.

12.5.1. Analysis Population

All study participants will be included in the analysis population. Intention-to-treat analysis will be performed and statistics for sub-groups containing no missing data or non-adherence will be included.

12.5.2. Analysis Plan

Secondary outcome data as described in **Section 10.3 – 10.9** will be characterized in terms of distributional characteristics such as the maximum, mean, median, and variation (as 95% confidence interval). Numerical scores (weeks to 50% and 75% graft healing, operative time, nipple projection, nipple diameter, NAC sensitivity, weeks to NAC vascularization, and LIKERT survey scores) will be characterized in terms of distributional characteristics such as the maximum, mean, median, and variation (as 95% confidence interval). Measurements reported as categorical variables (infection) will be characterized

as a percent.

12.6. Sample Size

12.6.1. Accrual estimates

According to the Stanford STRIDE database, Between January 1 2019 and January 1 2020, 25 patients with a history of autologous reconstruction for breast cancer underwent nipple-areolar reconstruction. Thus, we expect patient accrual to be achievable within the desired study timeframe. If accrual falls short of expectations, the study duration will be extended.

12.6.2. Sample size justification

The proposed sample size of 15 patients is not intended to support definitive conclusions around our primary outcome measures, but rather will (a) provide support that the NAC graft is safe for marketing purposes, (b) will confirm our ability to gather the necessary data in an adequately powered larger clinical study in the future, and (c) provide preliminary estimates of the study measures and their associated variability, in part to better define sample size requirements for the larger study.

12.6.3. Effect size justification

This is a single arm (non-randomized study) thus effect size is not applicable. Previous literature indicates that NAC reconstruction can be a significant determinant of psychological well-being in breast cancer survivors.[4,5] In a recent study, 80.3% of women who underwent NAC reconstruction would encourage other women to undergo NAC reconstruction (n=107, no confidence interval given).[6] Women who have undergone NAC reconstruction have been shown to have significantly higher general (72.2% vs 52.8%, $P < 0.0001$) and aesthetic (70.5% vs 46.5%, $P < 0.0001$) satisfaction scores compared to patients without nipple reconstruction (n=490 NAC reconstruction, n=206 without reconstruction).[7] Furthermore, patients who underwent NAC reconstruction using the Cook Medical BD-NRC (n=82 reconstructions in n=50 patients) only retained 40% nipple projection at 12 months post-reconstruction (3.8 ± 1.5 mm, compared with 10.5 ± 2.2 mm 1 week after surgery).[12] Data from this trial will be compared to these historical figures to look for trends and inform future studies.

12.7. Criteria for future studies

Completion of the study without any serious adverse events, with a >95% healing rate, and with patient survey scores at or above previously published data on patients who have undergone NAC reconstruction, will indicate a positive study result and convince us to continue with a fully powered study. Retention of NAC projection at the level or superior to previously published results will be additional reason to proceed with a larger clinical study.

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APPENDIX A: Participant Eligibility Checklist

Protocol Title:	A Single Arm, Single Center Pilot Study Evaluating the Safety and Healing Time of the NACgraft™ for Nipple-Areolar Complex Reconstruction
Protocol Number:	
Principal Investigator:	Geoffrey Gurtner, MD

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	Yes	No	Supporting Documentation*
1. Patient is between 18 and 65 years of age, inclusive.	☐	☐	
2. Patient has undergone uni- or bi-lateral autologous breast reconstruction a minimum of 3 months prior to enrolling in the study.	☐	☐	
3. Patient agrees to not undergo NAC tattooing until completing the study (approximately 12 months after engraftment).	☐	☐	_____ Provider initials/Date
4. Patient agrees to sleep on her back until the graft(s) have healed (approximately 6 weeks).	☐	☐	_____ Provider initials/Date
5. Patient agrees to abstain from aspirin, smoking, alcohol (>2 drinks per day), or excessive caffeine (>300mg per day) until grafts healed (6 weeks).	☐	☐	_____ Provider initials/Date
6. Patient is able to understand and willing to sign an informed consent form.	☐	☐	_____ Provider initials/Date
Exclusion Criteria (From IRB approved protocol)			
1. Patient is currently smoking or using tobacco or nicotine products (i.e. patch, gum, or nasal spray) or has used such products in the past 12 months.	☐	☐	
2. Patient has a history of delayed wound healing.	☐	☐	

3. Patient has a Vitamin C deficiency.	☐	☐	
4. Patient has diabetes (Type I or Type II).	☐	☐	
5. Patient has any uncontrolled comorbidity.	☐	☐	
6. Patient has a body mass index <18.5 or >40 kg/m^2.	☐	☐	
7. Patient is currently receiving radiation or chemotherapy or received radiation to the breast wall.	☐	☐	
8. Patient has a history of prior NAC reconstruction.	☐	☐	
9. Patient has had NAC tattooing.	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this study, I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

APPENDIX B: Nipple Reconstruction Satisfaction Surveys

Nipple Reconstruction Satisfaction Survey: Pre-operative

You have undergone breast reconstruction after mastectomy and are about to undergo nipple reconstruction with the BioAesthetics NACgraft. The following questions are designed to determine how you are feeling at this time. Please answer each question. Thank you for your feedback.

	Male	Female				
What is your sex?						
	< 18	19 – 35	36 – 50	51 – 65	> 66	
What is your present age?						
	< 3 months	3 – 6 months	6 – 9 months	9 – 12 months	> 12 months	N/A
How long ago was your left breast reconstruction (if applicable)?						
How long ago was your right breast reconstruction (if applicable)?						
				Yes	No	
I agree to sleep on my back for 6 weeks after nipple reconstruction.						
I agree to abstain from aspirin, smoking, excessive alcohol (no more than 2 drinks per day), and excessive caffeine (no more than 300mg per day, or 3 cups of coffee) for 6 weeks after nipple reconstruction.						
I agree to not undergo nipple tattooing for 12 months after nipple reconstruction.						
	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree	N/A
I am satisfied with the shape of my new left breast.						
I am satisfied with the shape of my new right breast.						
I would undergo breast reconstruction again.						
				Yes	No	N/A
My left breast was eligible for a nipple-sparing mastectomy, but I chose to have my nipple removed.						
My right breast was eligible for a nipple-sparing mastectomy, but I chose to have my nipple removed.						

Nipple Reconstruction Satisfaction Survey: Pre-operative

	No Sensation	Low	Normal	High	N/A
What level of pleasant sensation do you have in your left breast?					
What level of pleasant sensation do you have in your right breast?					
What level of unpleasant sensation do you have in your left breast?					
What level of unpleasant sensation do you have in your right breast?					
I had a nipple-sparing mastectomy on my left breast. The sensation in my left nipple is					
I had a nipple-sparing mastectomy on my right breast. The sensation in my right nipple is					
Answer the following items as compared to before your mastectomy.	**Much Worse**	**Worse**	**About the same**	**Better**	**Much Better**
My sense of body image is					
My sense of self-esteem is					
My sense of well-being is					
My sex life is					
Answer the following items as compared to before your breast reconstruction(s).	**Much Worse**	**Worse**	**About the same**	**Better**	**Much Better**
My sense of body image is					
My sense of self-esteem is					
My sense of well-being is					
My sex life is					
	Strongly Disagree	**Disagree**	**Neither Agree nor Disagree**	**Agree**	**Strongly Agree**
Before my mastectomy, my nipples were the same size.					
Before my mastectomy, my nipples were the same color.					
Before my mastectomy, my nipples were symmetrical.					
Nipple reconstruction will complete my breast reconstruction.					
Nipple reconstruction will improve my body image.					
Nipple reconstruction will improve my sense of self-esteem.					
Nipple reconstruction will improve my sense of well-being.					
Nipple reconstruction will improve my sex life.					

Nipple Reconstruction Satisfaction Survey – Post-operative

You have undergone nipple reconstruction with the BioAesthetics NACgraft. The following questions are designed to determine how satisfied you are with the outcome. By checking ONE box in each row below, please indicate how satisfied with your nipple reconstruction operation today. Thank you for your feedback.

Postop Visit: ☐3 month ☐6 month ☐12 month ☐Other _____

	< 18	19 – 35	36 – 50	51 – 65	> 66
What is your present age?					

If you had bilateral nipple reconstruction, please answer the following questions for ONE side only. Then answer the same questions on the following page for the OTHER side.

Breast: ☐Right ☐Left	**Strongly Disagree**	**Disagree**	**Neither Agree nor Disagree**	**Agree**	**Strongly Agree**
I am pleased to have had nipple reconstruction.					
I am pleased with the position of my reconstructed nipple.					
I am pleased with the overall appearance of my reconstructed nipple.					
I am pleased with the symmetry of my reconstructed nipple.					
I am pleased with the color of my reconstructed nipple.					
I am pleased with the softness of my reconstructed nipple.					
I am pleased with the appearance of my reconstructed nipple when nude.					
I am pleased with the appearance of my reconstructed nipple when clothed.					
I am pleased with the size of my reconstructed nipple.					
I am pleased with the projection (sticking out) of my reconstructed nipple.					
My reconstructed nipple made my new breast look better.					
	No Sensation	**Low**	**Normal**	**High**	
What level of pleasant sensation do you have in your reconstructed nipple?					
What level of unpleasant sensation do you have in your reconstructed nipple?					

Nipple Reconstruction Satisfaction Survey – Post-operative

If you had bilateral nipple reconstruction, please answer the following questions for the other side.

Breast: ☐Right ☐Left	**Strongly Disagree**	**Disagree**	**Neither Agree nor Disagree**	**Agree**	**Strongly Agree**
I am pleased to have had nipple reconstruction.					
I am pleased with the position of my reconstructed nipple.					
I am pleased with the overall appearance of my reconstructed nipple.					
I am pleased with the symmetry of my reconstructed nipple.					
I am pleased with the color of my reconstructed nipple.					
I am pleased with the softness of my reconstructed nipple.					
I am pleased with the appearance of my reconstructed nipple when nude.					
I am pleased with the appearance of my reconstructed nipple when clothed.					
I am pleased with the size of my reconstructed nipple.					
I am pleased with the projection (sticking out) of my reconstructed nipple.					
My reconstructed nipple made my new breast look better.					
	No Sensation	**Low**	**Normal**	**High**	
What level of pleasant sensation do you have in your reconstructed nipple?					
What level of unpleasant sensation do you have in your reconstructed nipple?					

Nipple Reconstruction Satisfaction Survey – Post-operative

Please answer the following questions ONCE

Answer the following items as compared to before your mastectomy.	**Much Worse**	**Worse**	**About the same**	**Better**	**Much Better**
My sense of body image is					
My sense of self-esteem is					
My sense of well-being is					
My sex life is					
Answer the following items as compared to before your nipple reconstruction(s).	**Much Worse**	**Worse**	**About the same**	**Better**	**Much Better**
My sense of body image is					
My sense of self-esteem is					
My sense of well-being is					
My sex life is					
	Strongly Disagree	**Disagree**	**Neither Agree nor Disagree**	**Agree**	**Strongly Agree**
I am pleased with my body image.					
I am pleased with my sense of well-being.					
I am pleased with my level of self-esteem.					
I am pleased with my sex life.					
I would choose to undergo this type of nipple reconstruction again.					
I would recommend this type of nipple reconstruction to another woman.					
I feel nipple tattooing is necessary in addition to my nipple reconstruction.					