PROTOCOL AND STATISTICAL ANALYSIS PLAN

Study Title: **Comparison of One-Port and Two-Port Tissue Expanders for Breast Reconstruction**

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1. Background

1 in 8 women in the United States will develop invasive breast cancer, and of these women, 35-40% will be treated with a mastectomy. Subsequent breast reconstruction has benefits for self-esteem and quality of life (Albornoz). In 2013, over 95,000 reconstructive breast procedures were performed, 75,000 of which were expander/implant based reconstruction (ASPS).

The majority of breast reconstruction procedures are done in a staged manner. Tissue expanders are placed at the time of mastectomy**.** These are then used to stretch the remaining skin to allow for eventual placement of an implant at the second stage of reconstruction. The simultaneous use of acellular human dermal matrix (ADM) as an internal sling to support the expander is frequently used because of aesthetic benefits, reduced capsular contracture, reduced amount of submuscular dissection and decreased time to complete the reconstruction (Breuning, Sbitany). With increased use of dermal matrices, increased complications have been documented, particularly infection and/or seroma, with rates up to 12-18% (Chun, Antony, Kim, Wiechman, Selber) and relative risks of 2.47-2.73 (Kim). Complications can necessitate further surgical procedures, hospitalization and removal of the tissue expander, or the need to abandon reconstructive efforts. Methods to reduce these complication rates would have substantial benefit for many breast cancer survivors.

Seroma formation is thought to be caused by an inflammatory response to the biological material acting as a (initially) non-vascularized foreign body. The presence of a seroma under the mastectomy skin flaps can lead to increased incidences of wound dehiscence, infection and/or asymmetry in the reconstructed breast appearance, both of which can lead to removal of the expander.

Authors have described modifications in technique designed to minimize seroma formation. These include placing an additional drain to drain the sub-ADM space as well as the sub-mastectomy skin flap space, leaving these drains in longer by lowering the threshold volume per 24 hour period, and applying postoperative soft compression dressings (Ganske).

Traditional management of an established postoperative seroma consists of percutaneous aspiration, seroma catheter placement and/or operative exploration, irrigation and drain replacement. Operative management is used for seromas refractory to aspiration or for suspected infected seromas. Imaged percutaneous drainage can also be used for aspiration and/or drain placement and cultures of the fluid can be obtained. Even with this technique, persistent fluid collections and infection can still necessitate expander removal (Tong). The presence of seroma fluid is linked to other complications such as infection and skin flap necrosis (Brzezienski). Thus, successful management of this complication may decrease other associated complications and the need to abandon the reconstructive efforts.

Methods to reduce and treat complications have focused on operative technique and not on the tissue expander itself. The AlloX2 tissue expander has been developed specifically to reduce and treat these complications. The traditional tissue expander has a single port to allow injection of saline through the skin directly into the expander for gradual stretching of the overlying skin. The AlloX2 expander has the same injection port plus a second port which is connected to a perforated drain placed on the lower edge of the expander (see attached diagram). The location of both ports are identified by a magnet placed over the breast skin. This second port gives percutaneous access to the peri-expander space, thus allowing removal of seroma fluid under the mastectomy skin flaps. Seroma aspiration using this access port in the expander is safer than percutaneous aspiration, as it will reduce the potential for accidental puncture of the expander during standard percutaneous drainage. The aspirated fluid can be cultured in the setting of infection allowing identification of bacteria and determination of antibiotic sensitivities. Additionally, instillation of culture specific antibiotic solutions directly into the peri-expander space can be accomplished through the second port. Thus, use of this second port in the expander can be both diagnostic as well as therapeutic.

The AlloX2 expander is FDA approved, but randomized prospective controlled studies have not been done comparing it to the standard single port expander for equivalency. The ability to decrease reconstructive failures related to seromas will benefit patients undergoing post-mastectomy reconstruction and potentially will reduce the costs involved in treating complications.

FDA Indications for Use: 510(k) Number K140383 (letter attached)

"AlloX2 Tissue Expanders are intended for temporary (less than six months) subcutaneous or submuscular implantation to develop surgical flaps and additional tissue coverage required in a wide variety of applications, particularly to aid in reconstructions following mastectomy, to aid in the treatment of underdeveloped breasts and to aid in treatment of soft tissue deformities.

Additionally, the AlloX2 Tissue Expanders contain a silicone drain component which allows access to and drainage of latent fluids from the periprosthetic space. This drain component does not replace short-term, immediate, intraoperatively placed drains." (FDA)

2. Objectives

The goal of this study is to compare the AlloX2 expander with the traditional single port expander for equivalency. Complication rates that will be tracked include seroma, mastectomy skin flap necrosis, infection, wound dehiscence, need for explantation of the expander. Management of seromas will be compared between the two groups. We hypothesize that the AlloX2 expander will be as effective in achieving the final outcome of completion of the second stage of reconstruction with equal or improved complication rates.

3. Study Design

A prospective 1:1 randomized, single center, open label study will compare the traditional 1-port tissue expander with the AlloX2 2-port expander placed during immediate tissue

expander breast reconstruction. Due to the nature of the surgery, the study cannot be blinded. Patients will be followed until completion of expansion and exchange for the permanent implant which typically takes 2 to 3 months. Risks factors that have been previously identified to be associated with increased postoperative complications include smoking, obesity, breast size, diabetes, radiation therapy, and expander fill volume will be identified. The final outcome is completion of expansion and exchange to permanent implant.

Standard operative procedure and postoperative care will be done. Both groups will have the same to external drains placed which is standard operative procedure. Complications will be noted at each postoperative clinic visit and entered into a database. Complication rates will be compared between the two groups and associations with risk factors will be analyzed. There will be no cross-over into the other group in case of reconstructive failure. Treatment failures will be treated in the same fashion in the two groups.

4. Study Population

The study patients will be recruited from the University of Kentucky Plastic Surgery clinic. They will consist of patients referred for breast reconstruction following mastectomy(ies), unilateral or bilateral, for breast cancer or for positive gene mutation. Only patients who are suitable candidates for and who agree to undergo tissue expander/implant reconstruction will be offered participation in the study.

The anticipated number of patients to be enrolled is 60, 30 randomized to each type of expander. The proposed study period for enrollment is January 2016 – December 2016.

Exclusion criteria include age less than 18, patients who refuse expander/implant reconstruction, patients who are not medical candidates for expander/implant reconstruction from a soft tissue standpoint, patients who are anticipated to need postoperative radiation therapy. Non-English speaking individuals or decisionally impaired individuals will not be enrolled.

The study will not involve fetuses, neonates, children, pregnant women, prisoners, or institutionalized individuals. Due to the nature of this study, only women will be enrolled as this is the population that undergoes mastectomy and breast reconstruction. Subjects will be chosen irrespective of ethnic background.

5. Subject Recruitment Methods and Privacy

Patients will be recruited from the University of Kentucky Plastic Surgery Clinic. Lesley Wong, MD, will determine if a participant meets eligibility criteria and will approach the patients during regularly scheduled clinical appointments in order to assess if they are interested in learning more about the study.

Eligible patients will be those undergoing immediate breast reconstruction with tissue expanders following mastectomy. A patient's acceptance or declination to be a part of this study will not affect the type of reconstruction performed on the patient, or their care in any way.

No advertisements of any form will be used with this study.

6. Informed Consent Process

Patients will be asked to sign the consent form after the investigators fully explain the study and risks. This will be done prior to randomization into one of two groups. There is no waiting period between informing the prospective subject and obtaining consent. Voluntary consent may be obtained by the principal investigator (PI) (Dr. Lesley Wong), as well as collaborating investigators who are authorized to obtain informed consent. The consent will contain information in line with IRB guidelines as to a brief background for the study, reason for their inclusion, risks, potential benefits, insurance coverage for injury, confidentiality, rights of the participant to refuse or withdraw, and guarantee to continuity of care should they refuse to participate or withdraw from the study, access to information, and payment for participation.

Written informed consent from the participant will be placed in their medical record and documentation of the informed consent process will be placed in the participant's progress notes. A signed informed consent form will be obtained by the investigator. The participant will receive a copy of the informed consent form.

7. Research Procedures

The study patients will be randomized into one of two groups, one using the AlloX2 two port tissue expander and the other using the existing single port expander (Allergan™). The surgical procedure will follow standard acceptable guidelines for tissue expander reconstruction (Alderman). Patients will receive IV prophylactic antibiotics and the surgical site is prepped with chloraprep. The expander is placed under the elevated pectoralis muscle and an acellular dermal matrix which is pre-sterilized (Alloderm™). The initial volume in the expander is recorded. Two standard suction drains are placed in the mastectomy defect and are removed when the output is <20cc/24 hours over two days.

Patients will be followed weekly in clinic to observe for complications and expand the expander. Filling of the expander is done weekly, or at an interval acceptable to the patient. When the desired volume is achieved, the patient will be scheduled for expander replacement with the permanent implant. This procedure is the final endpoint for the study.

If a seroma is suspected and there are no signs of infection, the expander is accessed through the second port of the AlloX2. If seroma fluid is aspirated, the fluid is cultured. If a seroma is suspected and there are signs of infection, the seroma cavity is drained with the second port and appropriate antibiotics can be ordered.

Medical records are reviewed to collect patient demographics, co-morbidities (hypertension, diabetes), adjuvant/neoadjuvant chemotherapy, body mass index, smoking status, operative time, and area of dermal matrix used. Postoperative complications include seroma, infection, skin flap necrosis. Univariate analyses of independent variables will be done, with the use of dermal matrix and development of infection as the dichotomous dependent variable.

8. Resources:

The research procedures will be conducted at UK Chandler Medical Center and University of Kentucky Plastic Surgery Clinic E-101 (Wing C, First Floor) 740 S. Limestone Street, Lexington, KY 40536-0284. The participants will be followed by Lesley Wong, MD and her research team which includes physicians and certified nurse practitioners and clinical research coordinators during the study. Emergency medical equipment, medications, and supplies will be at the physician's disposal should the participant have an acute untoward reaction.

9. Potential Risks:

- ChloraPrep: Blistering, burning, itching, peeling, skin rash, redness, swelling, or other signs of irritation on the skin, swelling of the face, hands, or feet, trouble breathing. A severe allergic may occur and could lead to death.

- Allergan Natrelle Style 133V Tissue Expanders

General Known Risks: Any invasive surgical procedures has risks such as infection, hematoma, dysesthesia, postoperative pain and delayed healing.

Specific Known Risks:

Magnetic field. The MAGNA-SITE® integral injection site contains a rare-earth, permanent magnet. If you already have an implanted device that would be affected by a magnetic field (e.g., pacemaker, drug infusion device, artificial sensing device) you must not have a MAGNA-SITE® tissue expander implanted. In addition, patients with MAGNA-SITE® expanders in place should not undergo diagnostic testing with Magnetic Resonance Imaging (MRI).

Deflation. The expander and infection site may leak as a result of damage from surgical instruments or trauma. Deflation release the saline filling and will require surgery to replace the expander to continue with the expansion process.

Tissue damage. Tissue damage may occur if the overlying skin is too weak to tolerate the pressure of expansion. Tissue damage is most likely to occur with expansion against an unstable wound or tissue area, or expansion that occurs too rapidly, causing ischemia.

Extrusion. Extrusion of the expander may occur as a result of tissue damage. Extrusion may require removal of the expander.

Capsular contracture. The scar tissue that normally forms around any implanted device, including tissue expanders, may tighten and become firm around the expander. Capsular contracture may make expansion difficult and painful, and necessitate surgical intervention.

Premature explantation. Adverse reactions may require premature explantation.

Displacement. Shifting and rotation of the expander/injection site may occur. Displacement may make the injection site difficult to locate and require surgical intervention.

Effects on bone. Chest wall compression has been reported in association with the use of tissue expanders for breast reconstruction.

Changes in sensation. The expansion process may affect sensation. Sensation may increase or decrease, temporarily or permanently.

Discomfort/distortion. Tissue expansion in an intensive process that causes temporary discomfort and distortion.

10. Safety Precautions

Provisions to guard against the potential risks and discomforts discussed in section 9 are as follows: Every precaution to prevent a direct study injury will be taken by medical personnel and the investigators. Should an adverse or serious adverse event occur, the research participant will be followed by physicians, registered nurses and other research staff members for the duration of the participant's hospitalization and recovery. Routine care will be provided by hospital staff. Emergency medical equipment, medications and supplies will be at the physician's disposal should the participants have an acute untoward reaction.

All patient information used in this study will be de-identified for purposes of the study. Once enrolled in the study, the patient's identifiable information will be replaced with a study number and will be followed using this number in all recording and correspondences throughout the study. Only the PI and the PI's team will have access to identifiable information prior to the patient's enrollment into the study.

11. Benefit vs. Risk:

There is no guarantee that a participant will receive any benefit from taking part in this study. The information from this research may decrease complications associated with breast reconstructive efforts. This may benefit society in the future and is not expected to benefit the individual subject. The risks to subjects are no greater than those from the surgical procedure alone and are reasonable in relation to the importance of the potential knowledge to be gained.

12. Available Alternative Treatments:

If participants do not want to take part in the study, there are other choices such as:

- No reconstruction
- Use the existing single port expander
- Autologous tissue reconstruction

13. Research Materials, Records, and Privacy:

For all participants, records from University of Kentucky Plastic Surgery Clinic will be reviewed to determine study inclusion by Dr. Wong. Participants will be given a unique numerical identifier to be used to link Protected Health Information to study data, assigned by the principal investigator. Protected Health Information will be kept in a separate password protected file on the desktop computer of the principal investigator, accessible only to the principal investigator and members of the research team. The computer is in a locked office. Demographic data on age (year of birth), race, gender and past medical history

will be collected from all participants. This data will be stored in a password protected spreadsheet kept on the desktop computer. Although all data will be entered on to the computer a printed copy of the datasheet is available upon request. Data collected from the study will be linked to the numerical identifier and tabulated in a coded chart so as to keep the participant's personal information private.

14. **Confidentiality:**

Data will be stored on the office computer of the principal investigator in password protected files. The office is located in the Kentucky Clinic, Division of Plastic Surgery, 740 S. Limestone, Lexington, KY 40536. Following review of all records and completion of data collection, all files containing Protected Health Information will be deleted so that no link exists between the data and the participant identifiers. No personal identifiers beyond name and medical record number will be stored. Data collected are automatically entered into a spreadsheet table using numeric identifiers only used in analysis, further diminishing any link Protected Health Information. This includes any and all dates, which cannot be back calculated. The protected health information will be destroyed within six months of completion of the study.

We will make every effort to keep confidential all research records that identify the participants to the extent allowed by law.

Participant information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. Participants will not be personally identified in these written materials. We may publish the results of this study; however, we will keep the participant's name and other identifying information private.

Electronic data with PHI are stored in the University of Kentucky's medical database that has limited medical personnel access, is password protected, and monitored for abnormal activity. Incidental materials containing participant identifiers will be shredded or incinerated.

Officials of the Food and Drug Administration, the University of Kentucky, and the manufacturer of the AlloX2 expander may look at pertinent portions of the records that identify the participant.

15. Payment

No incentives or monetary payment will be given in this study.

16. **Costs to Subjects**

Either the participant or their insurance company, Medicare or Medicaid will be responsible for the costs of all care and treatment a participant receives during this study that they would normally receive for their condition. These costs that are considered medically reasonable

and necessary and will be part of the care a patient would receive if they did not take part in this study.

The manufacturer of the AlloX2 expander is not offering any indemnification for their device as there are no increased risks over the other currently available types of expanders.

17. Data and Safety Monitoring: Not applicable

18. Subject Complaints: Participants are free to ask any question they may have about the study. Participants will be directed to the Principal Investigator if complaints, concerns, or questions arise and provided with contact information. Participants will also be advised to contact the staff of the Office of Research Integrity at 859-257-9428 or toll free at 1-866-400-9428 with any concerns.

19. Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture: Not applicable.

20. HIV/AIDS Research: Not applicable

21. PI-Sponsored FDA-Regulated Research: Not applicable.

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