Trial registration

Trial Registration Information	
Primary registry	ClinicalTrials.gov
NCT number	TBD
Primary Sponsor	University of British Columbia
Contact for scientific and public queries	Dr. N. Van Laeken, email: Nancy@vanlaeken.com
Public Title	The BREAST Trial: a randomized comparison of the surgical outcomes from four ADM products utilized in breast reconstruction
Scientific Title	The BREAST Trial: A randomized, non-inferiority, pilot study comparing the complication profile of four commercially available acellular dermal matrixes used in alloplastic breast reconstruction
Country of recruitment	Canada
Subjects	Patients undergoing alloplastic breast reconstruction with the use of acellular dermal matrix for breast pocket creation
Intervention	Active comparators: AlloMax or DermACELL or FlexHD, Alloderm
Study Type	Interventional, randomized, parallel, single blinded, pilot study
Date of first enrolment	November 2020
Target sample size	40 participants for pilot (328 for complete trial)
Recruitment status	Actively recruiting
Primary Outcome	Proportion of clinically significant seromas
Key Secondary Outcomes	Incidence of complications (hematoma, capsular contracture, implant loss), time to drain removal, number of seroma aspirations, Subjective assessment of cosmetic outcomes, Evaluation of the satisfaction and quality of life of patients undergoing breast surgery using the BREAST-Q

The BREAST Trial: A randomized, non-inferiority, pilot study comparing the complication profile of four commercially available acellular dermal matrixes used in alloplastic breast reconstruction

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Title

The BREAST Trial: A randomized, non-inferiority, pilot study comparing the complication profile of four commercially available acellular dermal matrixes used in alloplastic breast reconstruction

Funding

This trial has received funding from the BC provincial society of Plastic surgeons for administrative support as a single bursary through their research support initiative. No commercial funding or external funding sources have contributed to the development or conduction of this clinical trial. The design, management, analysis and reporting of the study are entirely independent of the manufacturers of Alloderm, FlexHD, AlloMAX and DermACELL.

Study design

The BREAST trial is designed as a randomized patient, non-inferiority trial with four parallel groups and the primary endpoint of proportion of post-operative seromas. Randomization will be performed in block randomization with a 1:1:1:1 allocation.

The study will be initially conducted as an internal pilot and then subjected to an internal review with preliminary data analysis. Formal protocol modifications will be made as needed followed by resubmission to UBC Rise ethics review board. Upon ethics approval, the study will be concluded with the goal of recruiting the entire desired study population. Our target patient population for the internal pilot study will be 40 patients within the study parameters of the protocol outlined below.

Intervention arms of comparison

Type of ADM:

- AlloDerm (LifeCell Corporation, USA)
- DermACELL (LifeNet Health, USA)
- Flex HD (Ethicon, USA).
- AlloMax (Bard Davol, USA)

Primary outcome: Proportion of clinically significant seromas
Time to completion: 1 year as an internal pilot study, 3 years as a formal RCT
Anticipated start date: 2020

Section 1.0: Introduction

Background

Breast cancer is the most commonly diagnosed female cancer in Canada and has a relatively high five-year net survival rate ranging from 84-88% [1]. With organized screening programs, the majority of breast cancers are being detected at an early stage (Stage I or II), which permits reconstructive opportunities for patients[1]. Reconstruction rates are currently rising [2], and between the years of 2000-2017, an increase of 35% in the annual rate of these procedures was reported by the American Society of Plastic Surgeons[3]. Specifically, alloplastic breast reconstruction is now becoming the standard of care as immediate implant-based breast reconstruction continues to increase in frequency [4].

The increased rate of alloplastic breast reconstruction can be attributed to the expanding utilization of Acellular Dermal Matrices (ADMs). ADMs are donated cadaveric dermis that is aseptically processed or sterilized in order to remove cellular and immunogenic components to prevent host reactions[5-8]. The use of human ADMs in breast surgery was first described in 2001 by Duncan [9] to reduce rippling of breast implants and later by Breuing and Warren in 2005 for breast reconstruction as a sling to support the lower pole of the breast [10]. ADMs were used in approximately 65% of breast reconstructive surgeries in 2017 and this rate continues to rise [11].

Benefits of acellular dermal matrices include facilitating single stage immediate direct to implant reconstruction [8, 12, 13] allowing for better coverage at the inferior pole of the breast[7, 14] along with: shorter expansion times with TEs [7, 12, 13, 15], lower capsular contracture rates[8, 12], and improved cosmesis including better implant positioning, IMF placement and IMF definition [7, 8, 12-14]. Furthermore, there is no associated donor site morbidity associated with ADM use [14]. However, the benefits of ADMs must be considered against an increased risk of ADM associated post-operative complications. Specifically, ADMs have been linked to an increased risk of infection, post-operative seroma [7, 12, 15], and delayed healing or mastectomy flap necrosis [14, 15] when compared to breast reconstructions without ADM use. Other complications such as implant loss, unplanned return to the operating room, or overall complication rate[15] were not influenced by the presence of an ADM. Additionally, cost is a commonly reported disadvantage to using ADM's [7, 12] as a single sheet values for multiple thousands of

dollars. Recently, Macadam and Lennox performed a cost analysis which, demonstrated that direct to implant reconstruction using an ADM is less expensive than to a two-staged reconstruction[16]. Similar cost effectiveness was demonstrated by de Blacam et al. [17] who noted that potential benefits of minimizing surgical stages in breast reconstruction justify the upfront costs associated with ADM use. Overall, the proponents of ADM use claim that the benefits outweigh the risks in immediate breast reconstruction[7] as ADM associated complication rates have generally decreased and stabilized as surgeon experience with these products has increased [8].

AlloDerm (LifeCell Corporation, USA) was the first ADM's to be described in literature and was one of the first ADM to be available in Canada in 2009 [18]. As a result, there is extensive literature regarding its use and safety in breast reconstruction[5, 7, 8, 13, 14, 19]. Since the introduction of AlloDerm, alternative products have been introduced including AlloMax (Bard Davol, USA) in 2010 [18], DermaACELL (LifeNet Health, USA) and Flex HD (Ethicon, USA). However, the benefits and risk of alternatives are less well described.

Flex HD was first compared to AlloDerm by Liu et al. where a multivariate analysis suggested that Flex HD may be an independent risk factor for implant loss but acknowledged their study was small and retrospective in that its reliability is only as accurate as its medical records. Additionally, the complication rates, including return to the OR, were similar between groups. Overall, they suggest a randomized controlled study should be conducted to clarify the risk and benefits [14]. In a study done by Ranganathan, Flex HD was found to be at increased risk of both minor and major infections when compared to AlloDerm. However, this study has been criticized for its low volume over a 15 year period and failure to state which Flex HD product was used – structural or pliable – of which Flex HD pliable is indicated for breast reconstruction[7]. Similarly, to Liu et al, they did not find any difference in return to OR rates[7, 14]. Other studies have since shown that there is no difference in complication rates between AlloDerm and Flex HD[8, 19] with one demonstrating that Flex HD has significantly lower post-operative implant extrusion and a higher cosmetic score[19].

DermACELL was found to be appropriate acellular dermal matrix option elucidated by Bullocks in 2014 [20]. It's decellularization process removes more than 97% of donor DNA with a sterility assurance level of 10^{-6} to reduce host reactions [5,

20, 21]. In a recent study comparing DermACELL to AlloDerm, there was statistically significant decrease in time to drain removal with DermACELL (regardless of immediate reconstruction or tissue expander placement) and higher incidence of Red Breast Syndrome in AlloDerm (26% vs. 0%)[5]. Other non-statistically significant differences included lower rates of hematoma, seroma, wound healing, infection and thus lower total implant failures[5]. However, this study is criticized as it was not used as per manufacturers guidelines and performed 'off-label' meshing of products. A small 9 patient clinical study using DermACELL was performed by Vashi and found low rates of seroma, infection and hematoma. However, the study involved a small sample size and may have been biased by the authors as they received compensation for data collection and analysis of the case series[21].

AlloMax, previously known as NeoForm, is a non-orientation specific [12] ADM that reports sterile processing techniques in contrast to aseptic methods. As a result, lower inflammatory reactions as seen in rat studies, may lead to lower complication rates[22]. Lower complication rates have been seen by Rundell et al. [13] and was demonstrated in a prospective study that examined tissue expander-based breast reconstructions over a 1 year period with 65 breasts. However, this study was criticized as there were 14 different breast surgeons performing mastectomies with variable flap thickness and different TE were used.

It is important to note that there are numerous ADM products available. Fenestrated ADMs are currently not part of the study design as the selected 4 products are based on surgeon familiarity and similarity of product characteristics to minimize potential confounding features. Minimizing the differences in products also preserves the external generalizability of our study results. However, should one of the products be found to have significantly different seroma outcomes early on (within the pilot study), there is the possibility to include a fenestrated product at that time to maximize study comparisons and study conclusions. Based on surgeon experience and literature support, contour fenestrated AlloDerm would be the fenestrated product chosen. Furthermore, this product could be incorporated into the study if one of the four products is deemed as being inferior to work with by the research team (ie. The surgeons develop a majority bias against one of the four products).

Rationale

At the present time, there is no high-quality evidence in the literature to aid in the decision-making process as to which ADM should be chosen based on patient clinical information. The results of this study may revolutionize the use of ADM's in breast reconstruction by improving both surgeon and patient knowledge of the post-surgical outcomes associated with the individual ADM types and improve subsequent informed decision making.

Given the increasing popularity of breast reconstruction with ADMs, medical companies have produced similar competing products. No large-scale randomized study has been conducted to directly compare the outcomes four ADM's in two-staged breast reconstruction. Therefore, there is no high-quality evidence elucidating safety and non-inferiority among products. This study aims to identify outcomes, complications, aesthetic results and patient satisfaction of four comparable ADM products. This will ultimately lead to the ability to directly compare ADM products and improved informed decision making for surgeons with respect to their use and anticipated outcomes. Given the significance of ADM associated complications and variability in the high cost of these products, a prospective direct head to head trial is justified.

Objectives

The objective of this study is to compare the safety and outcomes of four different acellular dermal matrices used in alloplastic breast reconstruction. The primary outcome will be: proportion of clinically significant seromas. Secondary outcomes will include: mean drain duration, mean aspirations per seroma, hematoma incidence, infection incidence, implant failure/loss, red breast syndrome, unplanned surgical care, rates of mastectomy flap necrosis, capsular contracture, ADM integration and cosmetic outcome. Additionally, using the BREAST-Q, patient satisfaction will be evaluated.

Hypothesis

1. There will be no difference in the proportion of clinically significant seromas (ie. requiring drainage/intervention) between the four acellular dermal matrix assisted breast reconstruction treatment groups.
2. Secondarily, there will be no difference in safety, complications, cosmetic, or patient reported outcomes when comparing four different human derived acellular dermal matrices.

Significance

Alloplastic breast reconstruction has shown a significant increase in popularity over the last 10 years. This is thought to be due to multiple factors including long term silicone implant safety data, increase in the frequency of bilateral mastectomies and improved cosmetic outcomes. Acellular dermal matrices (ADMs) were introduced in 2009 in Canada and have become increasingly popular as a critical component of alloplastic breast reconstruction following mastectomy. Currently, there is widespread data profiling the safety of ADMs, and numerous ADM alternatives to the original AlloDerm have been introduced. However, few high-quality comparative studies have been conducted to ensure the similar outcomes are obtained with ADMs other than AlloDerm. Clinical equipoise is thought to exist between four ADM subtypes: AlloDerm, FlexHD, DermaCell and Allomax, however this has yet to be effectively supported within the scientific literature. To date, there are no studies that compare four products in a randomized control trial fashion. Therefore, the purpose of this study is to identify product non-inferiority between ADM types.

Study Design

This study is a randomized control trial to be conducted in Canada from 2020 until 2 years post completion of recruitment. This study will include all patients who are agreeable and deemed appropriate for alloplastic breast reconstruction involving the use of an ADM with two stage tissue expander (TE) reconstruction. The ADM used will be determined by random assignment to one of four available products being utilized within the study: AlloDerm, AlloMax, DermACELL and FlexHD. Each ADM product will comprise of an individual treatment arm. Those undergoing bilateral reconstruction will have the same ADM used in each side. The four treatment arms will be compared to assess their impact on our primary outcome: proportion of clinically significant post-operative seroma requiring intervention. Analysis will be performed per surgeon to prevent post-operative outcomes from being confounded by the principle operator.

The trial will initially be conducted as an **internal pilot study**. We will initially target a study population of 40 patients for recruitment as a means to assess the feasibility of the study. In doing this, we will be able to establish the necessary protocol and administrative infrastructure that is needed to complete the trial in its entirety. We will also be able to create a sample population for initial outcomes

assessment in support of our selected outcome metrics. The initial data collection and review will be used to validate our study power calculation and ensure the appropriate study population sized is targeted for when the study transitions into a formal RCT.

Section 2.0: Methods Participants, Interventions and outcomes

Study Setting

The study will take place at four health centers affiliated with the University of British Columbia and the UBC breast program: the Vancouver general hospital (VGH), Mount Saint Joseph's hospital (MSJ), Saint Paul's Hospital (SPH) and the University of British Columbia Hospital (UBC).

Study patients will be initially recruited through the outpatient clinics from one of the above listed hospitals. They will complete their surgical procedures through the operative sites of one of the listed hospitals. Standard scheduled ambulatory follow ups will continue for two year post-operatively at the site of initial contact with their designated surgeon.

Patient recruitment

The UBC Breast Reconstruction program involves several plastic surgeons whom in conjunction with general surgeons perform a number of mastectomy and alloplastic breast reconstructions. These operations are carried out primarily in four hospitals in the central Vancouver area as listed above (study site). The senior author performs over 100-150 breast reconstructions per year and therefore we would anticipate recruitment over 2 year period to allow for adequate sample size. Patient recruitment will occur until all four treatment arms have received their targeted participant populations or clinical equipoise is no longer maintained.

Patient recruitment will be conducted at the time of initial consultation for breast reconstruction. Currently, patients are referred by their surgical oncologists to the four participating surgeons within this study. These patients are then presented with a plan for breast reconstruction based on their demographic and oncological characteristics. Patients who seek out alloplastic breast reconstruction and are appropriate surgical candidates are then consented for this process in office and scheduled for an appropriate surgical date based on OR availability and the schedule of the treating surgical team (Surgical oncologist and Plastic surgeon).

Patients who are successfully scheduled for breast reconstruction will simultaneously be screened by a trained research assistant affiliated with the

BREAST trial to evaluate if these patients are appropriate study candidates based on the defined study inclusion and exclusion criteria. The assistant will then introduce the trial to the potential study candidate and explain the study in entirety with the aid of information sheets and resources made available to the patient. Agreeable patients will then sign a consent form that is provided to them by the in person medical office assistant who will then register the patient in the randomization process for the study. All documents will be stored in a confidential manner in locked cabinets at the study site of original recruitment. Patients will be provided a two-week period to decide if they would like to enroll in the study. Should a patient agree to join the study while out of office, the consent process would be coordinated at their next in-person follow up.

Study subjects

Inclusion criteria

All woman aged 21 years or older but less that 65 undergoing unilateral or bilateral mastectomy with alloplastic breast reconstruction using ADM will be invited to participate. Breast reconstruction must be done by means of a two staged process using tissue expanders and ADM-based reconstruction followed by tissue expander to implant exchange.

Exclusion criteria to participation of the study

1. Patients undergoing autologous reconstruction either at the time of mastectomy or in a delayed fashion.
2. Patients with a history of previous breast reconstruction procedures.
3. Patients with prior radiation treatment to the breast or with prior mantle radiation
4. Any patient with a contraindication to breast reconstruction
5. Patients undergoing an axillary node dissection with clearance
6. Patients with an allergy to Polysporin or any of its ingredients.
7. Patients with contraindications to any of the acellular dermal matrices:
    - DermACELL: Allergy to Gentamicin, Vancomycin[12]
8. The surgeon performing the breast reconstruction may also deem a patient ineligible if intraoperatively, there is evidence of significant mastectomy flap ischemia prior to the initiation of the breast reconstruction procedure.

Randomization

Prospective breast reconstruction candidates will be identified at the initial consultation. Once the decision has been taken to perform alloplastic reconstruction,

the study will be discussed with the potential participant but a trained research assistant who will facilitate the consenting process. Patients that consent to proceed as study participants will then be registered into the centralized study database and randomization process.

Randomization will be performed in blocks at a ratio of 1:1:1:1. A web-based randomization program (REDCap) will assign a patient to one of four potential ADM groups (AlloDerm, AlloMax, DermACELL and Flex HD). This information will be non-blinded to the surgical staff who will then proceed to order the appropriate ADM product to be available at the time of the study participants scheduled breast reconstruction. Additionally, randomization will occur independently for each surgeon prevent bias from arising as a result of the surgeon performing the reconstruction.

Blinding

All patients will be blinded to the type of ADM selected upon by the randomization process. The surgeon performing the procedure as well as the operating team however will be aware of the ADM being used as the preparation of each ADM are different. Additionally, the operating team will remain unblinded to the selected ADM to ensure accurate documentation and to facilitate appropriate communication during the process of ADM transfer to the sterile operating field and subsequent implantation. Patients will be informed of the ADM product they received on the completion of the study.

Interventions

Surgical procedure

Patients involved in the study will present to the operating room having been previously randomized to one of four treatment arms: AlloDerm, AlloMax, DermACELL, or FlexHD. The surgeon will be aware of which ADM product that the patient has been randomized to and this will be reviewed at the initiation of the surgery at the surgical time out to ensure the correct product is available within the room and appropriately ready for use. The surgeon will have also ordered the product in advance as per the randomization process. Patients will firstly undergo either a bilateral or unilateral skin or nipple sparing mastectomy by a surgical oncologist. In addition, they may perform nodal sampling or axillary clearance if deemed necessary, as per standard of care. If axillary dissection and clearance is performed, the patient will be excluded from the study. The plastic surgeon will then perform alloplastic breast reconstruction raising a sub-pectoral pocket as per standard practice. All two

stage breast reconstructions will place smooth tissue expanders during the first stage of reconstruction. The inframammary crease will be recreated with a sling of acellular dermal matrix using the assigned ADM product. The standard size of ADM of 6 x 16cm will be used and will not be subjected to fenestration. Two drains will be placed, one in the mastectomy pocket superficial to the ADM and pectoralis muscle and one laterally. All patients will receive preoperative antibiotic therapy with Ancef as per standard elective indications for surgical site infection prophylaxis. All patients undergoing an alloplastic 2-stage reconstruction with tissue expander will have the subsequent second stage implant exchange after a minimum of 3 months following the first stage tissue expander insertion.

Radiation status

The patient's oncology team will deem if radiation treatment is necessary for an enrolled patient. Patients who are subjected to radiation during their breast oncology care will not be excluded from the study. If radiation is required after they have completed their stage I procedure, their implant exchange will be delayed a minimum of 6 months (standard practice of care) following insertion of the tissue expander.

Patient who require radiation will be analyzed within a subgroup analysis to ensure that this oncologic treatment factor is accounted for and to minimize the impact of this variable on study conclusions. Presence of radiation treatment will be included in the study as this treatment composes a large element of breast oncological care and outcomes specific to this population are of interest. The study analysis will be appropriately conducted to minimize confounding outcomes and the study statistician will be principally involved in this process. Furthermore, we suspect that patients who receive radiation may have unique aesthetic outcomes and satisfaction scores. This data be compared to non-radiated patients and compared amongst ADM products within this radiated population.

Post-operative treatment

Patients will be transferred to the post anesthesia care unit and then to the inpatient ward until they meet the usual discharge criteria. After discharge, all patients will receive a course of oral antibiotics until drains removed. Follow up will be performed in plastic surgery offices where progress will be documented using study affiliated data collection forms with defined relevant outcome details and post-operative course.

Sample size:

As there are four treatment arms within this study, a power calculation was conducted to identify the anticipated participant recruitment required to demonstrate a meaningful difference between study groups using our primary outcome. Power calculation was supported by a consulting epidemiologist (P.B.).

Our primary outcome is the proportion of patients that develop a clinically significant seroma requiring intervention. A clinically significant seroma is defined as one that necessitates drainage, either due to symptomatic concerns or clinical judgement by the evaluating surgeon. Drainage is achieved either through office-based aspiration or by ultrasound guided aspiration through radiology referral. Post-operative seromas occur in approximately than 10% of breast reconstruction cases when an ADM is utilized. We believe that incidence of seroma formation is an appropriate primary endpoint due to the clinical implication that the rate of seroma occurrence has on ADM selection. If an ADM product is associated with a higher incidence of post-operative seromas, surgeons would be dissuaded from utilizing this product even when cost differences are present.

For comparison between the ADM subtypes, we have chosen a difference of 10% in the proportion of clinically significant seromas. This is a clinically relevant difference that would guide the choice of product by surgeons. Therefore, for the power calculation, a mean of 0.10 with a margin of 0.10 will be utilized. Additionally, we will require an 80% probability (Beta=0.80) for 90% confidence (alpha = 0.10) for our statistical comparison. Using these parameters, a minimum of 82 patients per intervention arm is required to effectively power the study (328 total). A p-value of 0.10 allows for an attainable and reasonable target sample size for the purposes of the study. A p-value of 0.05 would require a significantly larger target population to ensure the study is appropriately powered which may become challenging given the number of study arms (4 ADMs). However, after completion of the internal pilot study this will be subjected to internal review with consultation from our team statistician and modified as needed.

As the trial will be initially conducted as an internal pilot study, only 40 patients will be recruited during this phase of the study. These patients will formally enter the study and receive their breast reconstruction within the parameters of the study protocol. An interim study analysis will then be performed on this initial sample population prior to proceeding out of the pilot phase of the study. Changes to the target study size will be made if the interim analysis suggests that this is

necessary to appropriately power our study using our primary outcome of proportion of seromas.

Section 3.0: Methods Data collection, management and analysis

Data Collection and Measured outcomes

All clinical data will be obtained prospectively. Clinicopathological factors and identified metrics associated with patient outcomes will be recorded at each follow up visit. Follow up for patients during the first stage of the two staged tissue expander reconstruction will occur at: 1 week, 2 weeks, and then in two week intervals until the final expansion volume has been reached. Following the second stage where the tissue expander is exchanged for the final implant, follow up will occur at: 1 week, 2 weeks, 4 weeks, 3 months, 6 months, 1 year and 2 years. The scheduled follow ups are not study specific and are consistent with routine post-operative care.

Patient demographics and relevant risk factors will be recorded including age, comorbidities, past surgical history, smoking status, current medications, allergies, alcohol consumption, radiation history, chemotherapies, BMI, type of mastectomy, cancer type and cancer stage.

Reconstruction associated parameters will also be collecting including mastectomy weight, and permanent implant volume. The primary outcome and secondary outcomes of the study are summarized below.

Summary Table of Primary and secondary outcomes

Primary Outcome Measure:	
Seroma incidence	Incidence of seroma formation requiring intervention including aspiration in-office or ultrasound-guided drainage [Time Frame: within 6 months of stage I or stage II surgery]
Secondary Outcome Measures:	
Mean drain duration (Days)	Postoperative duration of drain placements [Time Frame: within 1 month of stage I or stage II surgery]
Mean drain output (ml)	Total volume of drain output until drain removal [Time Frame: length of time the post-operative drain remains in-situ]

Mean seroma volume (ml)	Total volume of seroma fluid aspirated until resolution of seroma Time Frame: within 6 months of stage I or stage II surgery]
Mean aspirations per seroma	Number of aspirations required for seroma resolution [Time Frame: within 6 months of stage I or stage II surgery]
Hematoma incidence	Incidence of hematoma requiring evacuation or aspiration [Time Frame: within 1 month of stage I or stage II surgery]
Surgical site infection	Incidence of surgical site infection requiring antibiotics or operative management [Time Frame: within 6 months of stage I or II surgery]
Implant loss	Loss of Implant for any reason (wound dehiscence, exposure, periprosthetic infection) [Time Frame: within 2 year of stage II surgery]
Red breast syndrome	Noninfectious erythema localized to the area of ADM reconstruction [Time Frame: within 1 month of stage I surgery]
Unplanned surgical care	Unexpected return to the operating room that was not planned at the initial visit for any reason [Time Frame: within 2 year of stage I or stage II surgery]
Mastectomy flap necrosis	Mastectomy flap necrosis and associated management: expectant, office debridement, or return to the operating room [Time Frame: within 1 month of stage I surgery]
Capsular contracture	Incidence of capsular contracture (as identified by the plastic surgeon, grouped by Baker's classification of severity) [Time Frame: within 1 years after stage II procedure]
ADM integration	Clinical assessment of ADM integration into the breast pocket at the time of the second stage

	procedure. [Time Frame: Specimen obtained at the stage II exchange to implant procedure]
Post-operative aesthetic assessment (patient and surgeon)	Subjective assessment of cosmetic outcome by the patient and blinded assessors using post-operative aesthetic breast survey assessment [Time Frame: within 2 years of stage II surgery]
Patient satisfaction	Evaluation of the satisfaction and quality of life of patients undergoing breast surgery using the BREAST-Q [Time Frame: within 2 years of stage II surgery]

Primary outcome:

Seroma formation occurs when serous fluid accumulates in the breast reconstruction surgical site post operatively resulting in a clinically appreciable pocket of fluid. The primary outcome measure of our study is: proportion of post-operative seroma requiring clinical intervention.

The seromas themselves are detected clinically when patients present for post-operative evaluation that includes a clinical exam, which facilitate the seroma diagnosis. After the seroma diagnosis, they are commonly managed by percutaneous aspiration that can be performed in a clinic setting by the surgeon with local anesthetic. In the case of larger seromas, aspiration and drainage can be performed under ultrasound guidance. Rarely, seroma's that do not resolve by repeat aspiration require operative evacuation and re-closure of the surgical site.

The use of ADMs has been linked to an increase incidence in post-operative seroma formation in breast reconstruction patients [14, 23]. However, ADM use is also associated with a reduction in the risk of capsular contracture, a complication associated with scar tissue accumulation around the implant that distorts the aesthetics of the breast and can be painful for the patient. Therefore, this benefit of utilizing ADMs in breast reconstruction is weighted against the increased risk of seroma formation.

The incidence of seroma formation after breast reconstruction with ADMs remains low at less than 10%. Evaluating if ADM type is associated with different

rates of seroma formation is necessary to identify if these products can be used interchangeability. Surgeons have a low threshold for selecting a specific ADM product should there be variation in their complication profile. Even an increase in seroma incidence by as little as 5% may deter surgeons from selecting a product due to the negative impact seroma formation has on patient care and wellbeing.

A seroma will be defined as a collection of serous fluid that develops under the breast skin flaps following surgery. In the outpatient clinic, if patients express discomfort or present with a clinically significant seroma within their breast pocket, they will receive ultrasound-based or surgeon conducted aspiration. The secondary outcomes include mean aspirations per seroma until resolution, seroma aspiration volume measurements, and time to drain removal. These secondary outcomes provide additional information and statistics that can be used to profile the primary outcome.

If the gross estimation is less than 30 ml, or does not necessitate aspiration, the patient will be managed conservatively and monitored as per standard of care. Seromas that occur within 6 months post a surgical procedure will contribute to the primary endpoint analysis.

As the primary endpoint, the proportion of seromas that occur will then be subjected to statistical comparison between ADM subtypes. All statistical analysis will be conducted after being stratified by surgeon to ensure that the principle operator does not confound the association between ADM type and seroma incidence.

In conclusion, the decision to select the proportion of post-operative seroma requiring clinical intervention as the primary endpoint of the study is multifactorial. The first is that seromas themselves are clinically significant outcomes that influence post-operative care and their occurrence rate is directly increased by the presence of an ADM. Therefore, understanding the relationship between seroma occurrence and the different ADM products will influence product selection and outline complication profiles of these products. Seromas' and their associated interventional management are associated with elevated health care costs. Most importantly the presence of a seroma that require an invasive physician supervised procedure in order to establish resolution affects a patient's post-operative course. Associating ADM products to clinically significant seroma outcomes will help profile which ADM that have the largest impact on health care resources and patient care. Finally, one of the earliest

symptoms of a ALCL presentation is a delayed large volume seroma. Therefore, understanding seroma incidence and outcomes tied to breast reconstruction with ADMs is of paramount importance for long term implant associated care.

The pilot study again will be concluded by an internal review and should proportion of clinically significant seromas be deemed an inadequate primary outcome measure this will be subjected to reassessment and modification as needed.

Secondary outcomes:

Secondary endpoints that will be collected and incorporated into the study analysis include time to mean number of aspirations per seroma until resolution, seroma aspiration volume measurements, hematoma incidence, incidence of surgical site infections, implant loss, red breast syndrome, unplanned surgical care, incidence of mastectomy flap necrosis, incidence of capsular contracture, ADM integration, cosmetic evaluation and patient satisfaction.

The time to drain removal between the 4 treatment arms will be compared. Time to drain removal will be collected and recorded per breast. Patients will be instructed on how to empty and record their drain volumes. Drains will be left in situ until producing <30mls every 24 hours to a maximum of 2 weeks, or otherwise advised by the surgeon. Patients who require prolonged drain placement will be recorded for data monitoring purposes tied to the secondary outcome of drain management. Reasons for prolonged drain placement will be categorized as scheduling conflicts/missed appointments or as clinically indicated. The duration of the drain is to profile clinical practices around drain use.

The total volume of seroma fluid aspirated will be calculated for each seroma by the summation of aspirated volumes performed either through clinic aspiration of US guided aspirations. The total seroma volume will be recorded in milliliters within 6 months of each stage of the surgical procedure.

The total number of aspirations until seroma resolution for each seroma will be calculated by the summation of aspirations performed either in clinic or by US guidance. The total number of seroma aspiration will be recorded within 6 months of each stage of the surgical procedure.

Hematoma will be defined as an expanding mass of blood requiring evacuation in the OR or significant bruising noted at the 1st post-operative visit. The

volume will be quantified by operative evaluation or by ultrasound when possible if the hematoma is investigated by imaging. The total hematoma volume will be recorded in milliliters within 1 month of either surgical procedure.

Surgical site infections will be identified based on patient post-operative clinical status including signs of erythema, pyrexia, local tenderness or presence of purulent discharge on return to operating room[5]. These will be managed with wound culturing, appropriately selected antibiotics and return to the operating room if indicated. Cellulitis is defined as whole breast erythema, edema, local tenderness that resolves with oral antibiotics. A surgical site infection will be defined as peri-incisional erythema, pyrexia, local tenderness beyond cellulitis [5], requiring IV antibiotics with either a positive aseptically obtained culture or the presence of purulent discharge on exam or upon return to the operating room. Post-operative infections will be recorded within 6 months of both surgical procedures.

Implant failure or implant loss will be recorded when the removal of implant(s) in the operating room [5] occurs for pathological reasons, or findings of a ruptured implant. This will be confirmed intraoperatively or by imaging evaluation including MRI or US.

Red Breast syndrome, which is described as a delayed type hypersensitivity which is idiopathic, and self-limiting erythema, in the absence of other signs of symptoms of infection, in an otherwise asymptomatic patient. It is isolated to the lower pole of the breast in the distribution of the underlying acellular matrix, and is refractory to oral antibiotics and resolved without further complications[5, 24].

Any unanticipated to return to the OR will be noted. This will include the following indications: Seroma, Hematoma, Soft Tissue Infection, Mastectomy Flap Necrosis, exposed implant, capsular contracture, or animation that requires intervention. Unplanned surgical procedures will also include implant loss or rupture as defined above.

Mastectomy flap necrosis (MFN) is defined as vascular compromised skin flaps that require intervention. It will be record and quantified by size of surface area involved measured **in centimeter units.** The location will be documented by quadrant localization (UMQ, ULQ, LMQ, LLQ) and will be assessed for depth involvement (superficial, full thickness, indeterminate, exposed implant).

Photographs will be taken of identified necrosis and the subsequent surgical management will be recorded: conservative (with dressings and/or antibiotics) or debridement either in the office or operating room. If conservative management fails, and the patient requires debridement, their management status will be changed to the intervention given. To differentiate delayed wound healing from MFN, delayed wound healing is wound disruption that does not require surgical intervention, where MFN beyond superficial depth, requires sharp debridement and closure of skin [5]. MFN will be recorded within 1 month of the stage I breast reconstruction procedure.

Capsular contracture which is progressive hardening and thickening around the implant, will be recorded and classified according to Baker's classification. Grade I include breast that are soft without significant scar tissue. Grade II includes breasts with palpable scar tissue around the implant, however the capsule is not visible. Grade III includes visible and palpable hardening around the breast leading to a deformed breast shape. Grade IV includes breasts that are often cold, hard, and very painful to palpation. There are visible and palpable capsular deformities.

ADM integration will be evaluated clinically during the second stage procedure. The operating surgeon will inspect the ADM previously placed in both breast pockets and score the degree of integration on a 4-point scale. This scale has been adapted from Mendenhall et al., with 1 = 100% integration, 2=greater than 50% integration, 3= less than 50% integration and 4= 0% integration[27]. Additionally, punch biopsies will also be obtained from the ADM and subjected to pathological evaluation for angiogenesis and lymphogenic infiltration.

ADM biopsy specimens will be sent to pathology for microscopy assessment and to evaluate ADM integration. These specimens will be stored within the routine practices of the pathology department for oncological specimens (2 years for paraffin blocks). The study specimens will be disposed of by standard tissue disposal. Should the study be terminated early, the specimens will be disposed of. There is no future plan for utilization of these specimens.

An evaluation of the aesthetic outcomes of the four treatment arms will be performed. All patients will have 5 standardized photographs of the breasts between the levels of the shoulder and umbilicus in front of a uniform background with patients standing with their hands on their buttocks from 1 m away. The photographs will be taken at 5 angles: a frontal view, a view from each lateral side, and at 45˚ to

each lateral side. All photos utilized for aesthetic evaluation will be obtained 24 months postoperatively after the second stage reconstruction. The surgeons will be asked to score the aesthetic appearance using the Aesthetics items scale, which is a validated and reliable tool for assessing outcomes after breast reconstruction surgery[28], including volume, shape, symmetry, scars, and nipple (when applicable). All images will be viewed through an EMR system and not be sent off-site. Concurrently, the patient will also be asked to complete an aesthetic evaluation. Additionally, a sample of the last 5% of patients enrolled will have deidentified photos from each ADM group obtained and will be presented to a panel of blinded plastic surgeons. This evaluation will be performed as a single analysis after completion of the trial.

Patient satisfaction will be assessed to complete a BREAST-Q assessment prior to reconstruction and 24 months after the second stage reconstruction for patients with tissue expanders. This previously validated patient reported outcome measure that will allow for the ability to evaluate patient satisfaction, well-being and the impact of the breast reconstruction [29-31]. These outcomes will be collected for all treatment groups.

Statistical methods

Firstly, the patient demographic variables previously listed will be summarized for each treatment are and summarized to describe the study patient population. Continuous variables will be reported by mean ± standard error. All outcomes evaluated by this RCT will be done so using an intention to treat analysis. A stratified analysis will be done by surgeon between ADM subgroups.

To compare the primary outcome, the number of seromas for each ADM subtype will be tabulated. The number of seromas will be calculated per breast for each ADM treatment arm. An analysis of variance test (or Kruskal-Wallis) will be used to determine if a difference is detected within the treatment groups. Individual pair wise Wilcoxon rank-sum tests will then use used to compare between sets of ADMs and ultimately identify which ADM is associated lowest seroma rate. A p-value of less than 0.10 will be deemed statistically significant. A similar analysis will be conducted to additionally compare the output volumes from the drains between the treatment arms and the frequency of aspirations required for seroma management in the post-operative course.

The secondary outcomes outlined to be evaluated by the study comprise of the complication profiles of each ADM group and will be recorded by frequency and percent occurrence. Chi squared or Fisher's exact tests will be used when appropriate to compare categorical data between the treatment arms.

Analysis of the aesthetic evaluation using the Aesthetic item scale will be performed using a non-parametric test (Wilcoxon rank-sum) to compare Likert scale scores for each metric between the four treatment arms. This will include analysis of the overall scores assessed by the scale for each patient. Finally, the scores produced from each metric of the BREAST-Q assessment will be subjected to a similar comparison based statistical analysis between ADM groups.

Data Storage

As this study will be initially conducted as an internal pilot study, all patient associated data will be recorded using the appropriate data collection forms. These forms include a consultation form, pre-operative exam, post-operative follow up, surgical record form and a procedure log. These forms will be maintained within each surgeon's office in paper format so that they can be easy accessed by study personal. Studied affiliated charts will be stored in locked cabinets with the office space to ensure confidentiality. Individual surgeons will only have access to the study charts of the patients that they are directly involved in caring for. Our appointed research administer will be responsible to manually entering the data into REDcap which will be used for electronic storage and facilitating data analysis.

After completion of the internal pilot study, the study will be subjected to an internal review process to determine feasibility and likelihood of successfully obtaining of target study population size within our institution. If this review is successful we will transition the record collection process to be conducted entirely electronically using REDCap.

Harms and potential risks

In general, acellular dermal matrices have shown a trend for increased risk of infection and seroma but have also demonstrated a potential reduced risk of capsular contracture [7, 12, 14, 15]. The vascularity of the mastectomy flap in most cases has a significant effect on complications[6]. This is dictated by the general surgeon's ability to safely resect the pathology, whilst leaving behind a vascular skin flap.

Some of the acellular dermal matrices have been associated with an inflammatory reaction named red breast syndrome. This does not constitute and infection as the erythema is well demarcated and presents in a well-defined line overlying the acellular dermal matrix. This is self-limiting and does not require any change in management but higher rates have been noted in ready to use AlloDerm [5, 24].

These risks will be mitigated by the fact that the use of acellular dermal matrixes has been standard practice in alloplastic breast reconstruction. Currently all four surgeons participating in this study utilize ADM as the basis of their alloplastic treatment algorithm to improve the long-term outcomes of their patients and decrease the likelihood of capsular contracture. Only if patients have increased risk of mastectomy flap necrosis is the use of an ADM avoided. These principles will be maintained within this study. If at any time, the surgeon's preference is to not incorporate the use of an ADM into the patient's surgical plan, that patient will be removed from the study to facilitate their new care plan.

To ensure that clinical equipoise is not lost during the study, a blinded statistician will perform preliminary data analysis at designated time intervals. If at any point, one ADM demonstrates a difference in surgical outcomes compared to the others, the clinical trial will be abandoned.

Monitoring committee

The preliminary analysis of the 40 patients involved in the pilot study will occur by the Data and Safety Monitoring Board. This will determine feasibility for the full study.

Once the full study is initiated, there will be interim analysis performed every 6 months to ensure early identification of any safety concerns. If there is a notable difference in early outcomes and a loss of clinical equipoise, the trial may be terminated prematurely.

Section 4.0: Ethics and Consent

Confidentiality and Consent

All study information will be store at the study site of collection. Participant information will be stored in locked cabinets with restricted access. Data collection forms and associated study files will de-identified by assigning a participant code to

each study participants. A master file will be maintained solely by the research administrator of the study which will be password protected, encrypted and stored separately but would allow for decoding of the study participants should this be required for any reason.

Participant's study information will not be released outside of the study without the written permission of the participant.

Declarations of interests

JR, PM, TS: Have no discourses or conflict of interests to state. The remaining declarations of interests to be reviewed with all affiliated study members.

Research and ethics approval

The study protocol and all associated forms (e.g. data collection forms, consent forms and consultation forms) will be sent for review and approval by the IRB (institutional review board) of UBC under the human ethics committee.

After the initial review and approval by the IRB, annual review of the study protocol and auditing of study progression will additionally be performed. This process is maintained for ensuring ethics approval through the entire study duration. Completion of the study will be submitted to the UBC IRB within 3 months of study termination.

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