The Use of Acellular Dermal Matrix in One-Stage Implant Breast Reconstruction: A Multicenter, Randomized, Controlled Trial (Multi-centered Canadian Alloderm Trial-MCCAT)

Study Protocol and Statistical Analysis Plan

Jun 15, 2011

i. SPECIFIC AIMS

We are currently leading a multi-center randomized controlled trial (RCT) to study the impact of acellular dermal matrix (ADM) assisted one-stage implant reconstruction on quality of life and patient satisfaction. This trial was awarded funding by ASPS-PSEF in 2009 and has been actively accruing participants at two breast centers in Toronto, Canada since September 2009. To date, 67 patients have been successfully enrolled into the RCT and an interim analysis has revealed similar short-term complication rates between the one-stage ADM implant study arm and the two-stage TE/I control arm. To increase patient enrollment into the trial, we plan to open trial recruitment to Vancouver General Hospital, the highest volume breast cancer center in western Canada in January 2011. In addition, by eliminating the intermediate inflation process and a second operative procedure, we hypothesize that both the cost and its utility as valued by patients will be superior in the one-stage ADM method compared to the two-stage TE/I method. In addition to measuring postoperative morbidity and complications, patient perception of their health status (utility) is a paramount consideration in the cost effectiveness analysis (CEA). CEA will be performed on person-level cost (direct and indirect) and effect data (utility measured by Breast Q© and EQ-5D) using net benefit regression, a novel technique developed by our collaborator (J.H.).[2-4,16-22] A preliminary cost comparison that was performed for 10 randomly selected patients in our RCT has demonstrated that the average cost was $1,572 and $595.91 more expensive per patient for the two-stage TE/I than the ADM assisted one-stage method for unilateral and bilateral reconstructions respectively at University Health Network. The addition of a CEA follows the natural progression of scientific research and is the logical sister study to assess the resource costs of this new surgical intervention in the current climate of increasing resource restraints and financial responsibilities.

The **primary objective** of this study is:

1. To compare patient satisfaction and QOL between one-stage ADM and two-stage TE/I reconstruction without ADM following mastectomy. Patient satisfaction will be evaluated using the Breast Q© at two-weeks, as well as six months and one year following completion of reconstruction.

    Hypothesis: Patient satisfaction and QOL will be higher in the ADM assisted one-stage implant reconstruction group compared to the two-stage TE/I group at all three time-points.

The **secondary objectives** of this study are:

1. To compare the short- and long-term complication rates between the two techniques.

    Hypothesis: The use of ADM in one-stage prosthetic breast reconstruction is not associated with increased short- and long-term postoperative complications compared with the traditional two staged TE/I procedure.

2. To examine the overall aesthetic outcome achieved using the ADM facilitated one-staged breast reconstruction at six months and one year following completion of the reconstruction.

    Hypothesis: The overall aesthetic outcome achieved using the ADM facilitated one-stage breast reconstruction is superior to that following the two-stage breast reconstruction.

3. To perform a cost-effectiveness analysis (CEA) of the two reconstruction methods using the net benefit regression model on person-level cost and effect data collected during the study.

    Hypothesis: Both the direct and indirect cost will be reduced and patient-reported utility will be greater for the one-stage ADM method compared to the TE/I method.

ii. RESEARCH STRATEGY

iia. Significance

Breast reconstruction has been shown to have a positive impact on the self-esteem and quality of life (QOL) in women suffering from breast cancer.[5-10]The American Society of Plastic Surgeons has found the two-stage tissue expander/implant (TE/I) technique to be the most commonly used method of breast reconstruction.[1] The wide-spread acceptance of the two-stage reconstruction is due to the high complication rates (25% overall explantation rate) associated with the traditional method of one-stage immediate implant reconstruction.[11, 12] The primary drawback to the TE/I technique is that it requires two separate operations under general anesthesia and multiple clinic visits for expander inflation. We are currently leading a multi-center randomized controlled trial (RCT) to study the impact of acellular dermal matrix (ADM) assisted one-stage implant reconstruction on QOL and patient satisfaction. This trial was awarded funding by the ASPS-PSEF and has been actively accruing participants at two breast centers in Toronto, Canada since September 2009. Our primary hypothesis is that the ability to convert a conventionally two-stage procedure to only one step would not only theoretically improve patient satisfaction, decrease the morbidity associated with multiple expansions and a second operation, but justify the prohibitively high cost of this new biomaterial incurred by the patient, hospital or insurance company.

Therefore, in addition to continuing our rigorous investigation of ADM in one-stage breast reconstruction in a multi-center, randomized controlled trial on patient satisfaction and quality of life measured using the Breast Q©, we propose to expand the scope of our current project to include a **cost-effectiveness analysis**. By eliminating the intermediate process of tissue expansion and converting the conventional two-stage procedure to one-stage with the use of human acellular dermis, we hypothesize that in addition to the cost of the new surgical treatment being lower, its utility will also be found to be greater compared to the two-stage TE/I breast reconstruction method. The addition of a cost-effectiveness analysis to our current RCT follows the natural progression of scientific research and is the logical sister study to assess the resource costs of this new surgical intervention. Furthermore, to increase patient enrollment into the trial, we are seeking funds from ASPS-PSEF to add a third site, Vancouver General Hospital which has the highest volume of immediate prosthetic breast reconstruction in Western Canada. With the addition of this third Canadian site, we anticipate fulfilling patient enrollment of a minimum of 72 patients per arm of the study by August 2011.

iia – 1. Rationale for conducting a cost-effectiveness analysis

The heightened awareness in recent years of the need to operate within budgets in the health care sector has created the ideal climate for conducting cost-effectiveness analysis (CEA).[13] This is especially true for reconstructive surgery of the breast following mastectomy due to the large number of available techniques used.[14, 15] Furthermore, the success of plastic and reconstructive surgeries is measured only in a small degree by post-operative complications and morbidity but to a greater degree in terms of patient perception of their health outcome (utility). Paramount in the CEA, therefore, is considerations of patient satisfaction and quality of life. By eliminating the intermediate process of tissue expansion and a second operative procedure, we hypothesize that both the cost and its utility as valued by patients will be superior in the one-stage ADM method compared to the two-stage TE/I method. Cost effectiveness analysis will be performed on person-level cost and effect data using net benefit regression, a technique developed by our collaborator.(J.H.) [2-4]The cost data will come from hospital cost accounting systems and patient reports. The primary patient outcome measure will be the global Breast Q score and the secondary outcome measure will be quality adjusted life years (QALY) as measured by the EQ-5D. Our collaborator, Hoch and his research team have extensive experience with applying standard CEA methods [16-22]as well as developing new CEA methods [2-4].

iia – 2. Rationale for recruitment at a third Canadian center

Since our trial opened recruitment at University Health Network and Women's College Hospital, Toronto, Canada in September 2009, a total of 78 eligible women have been approached for the trial, and of these, 11 have declined. Patient refusal has been attributed to patient reluctance to undergo the randomization process; concerns about ADM safety and performance of a new surgical procedure. Although we have received over 50 internet enquiries regarding the clinical trial, most of these patients were from the USA and consequently not eligible for the trial. Lastly due to our stringent exclusion criteria with the aim of limiting complication rates, such as exclusion of all patients who have had prior breast irradiation or anticipated to receive postmastectomy radiation, breast ptosis greater than grade II, and desire reconstruction cup size greater than C, our adherence to these criteria have negatively impacted patient enrollment.

At the current patient accrual rate of approximately 6 patients per month at the two Toronto sites, it would take approximately another 13 months to achieve the necessary sample size of 72 patients per study arm (total of 144 subjects). Due to these considerations, we are proposing to recruit a third site, Vancouver General Hospital (VGH), the center with the highest volume of breast cancer care in western Canada. This center employs 3 reconstructive surgeons (PL, SM, and NVL) and treats 125 immediate alloplastic breast reconstructions per year. AlloDerm (LifeCell Corp. Branchburg, N.J.) has been approved for one-stage direct to implant reconstruction at VGH since March 1, 2010. Since that time, the two reconstructive surgeons (PL, SM) have performed more than 35 Alloderm assisted one-stage direct to implant reconstructions using a similar technique described by this protocol. Assuming that 60% of all patients interested in immediate alloplastic breast reconstruction are candidates for the trial (75 patient/year), and if 20% of the eligible candidates declined to enter the trial, VGH would still enroll approximately 60 new patients per year. Therefore, if we used a conservative estimate of recruitment of 5 new patients per month for Vancouver General Hospital, then combined with the two Toronto sites, it would take approximately only 7 more months (rather than 13 months) to complete patient accrual for the study.

iia – 3. Preliminary Data

Since our trial opened recruitment at University Health Network and Women's College Hospital, Toronto, Canada in September 2009, a total of 67 women have been registered into the trial. Fifty-one patients have been randomized to date, and the other 16 patients are still awaiting randomization. Randomization has been balanced between the one and two-stage procedure arms in blocks of eight and is stratified by study site as well as laterality of the reconstruction. Breakdown of patients randomized by site and laterality is outlined below:

University Health Network (N=33)	Unilateral	Bilateral
1 stage w/ AlloDerm/ Implant (N=17)	(n=7)	(n=10)
2 stage w/ TE (N=16)	(n=8)	(n=8)

Women's College Hospital (N+18)	Unilateral	Bilateral
1 stage w/ AlloDerm/ Implant (N=10)	(n=2)	(n=8)
2 stage w/ TE (N=8)	(n=2)	(n=6)

Preliminary cost-effectiveness analysis

The average piece of Alloderm (LifeCell Corp, Branchburg, N.J.) for one-stage implant reconstruction is thick and 6cm X12cm in dimensions, and costs $2105 in Canadian currency. Preliminary comparison of the two surgical techniques was performed by retrospectively reviewing all case costing data for 10 randomly selected study subjects who underwent either one-stage Alloderm or two-stage TE/I reconstructions as part of the RCT from November 2009 to September 2010 through the University Health Network Accounting Department. Our hospital's Accounting Department collects cost data for every ambulatory clinic visit, emergency department visit, surgery, and in-hospital stay. We found that there were on average 5 more clinic visits (TE inflation sessions) in the two-stage TE/I than one-stage Alloderm group. The average direct cost to the hospital was $1,572 and $595.91more expensive per patient for the two-stage TE/I than Alloderm assisted one-stage method for unilateral and bilateral reconstructions respectively. (APPENDIX 1)

Interim analysis of complication rates

An interim analysis of short-term complications revealed similar rates of postoperative complications between the two arms of the trial. In the one-stage Alloderm assisted implant study arm, the rate of major complications is 0 and the rate of minor complications is 7%. There has been 1 case of cellulitis and 1 case of infected seroma both successfully treated with antibiotics. In the two-stage TE/I control arm, the rate of major complications is 4% and the rate of minor complications is 12.5%. In this arm, there were 2 cases of cellulitis successfully treated with antibiotics, 1 case of incisional dehiscence managed with conservative dressing changes, and 1 case of infected seroma that resulted in premature removal of the expander.

iia – 4. Anticipated Impact

Consistent with the mission of the American Society of Plastic Surgeons to "***provide the highest quality patient care"***, this proposal represents innovative research whose aim is to rigorously compare outcomes between a well-accepted method of breast reconstruction with a novel technique using a new biological material in the setting of a RCT. We are requesting funds to support a **cost-effectiveness analysis** to accompany this ongoing RCT. Unlike most biologic innovations that improve health outcome at an additional cost to the healthcare system, the use of ADM may be found to be cost-saving as indicated by our preliminary economic analysis (Preliminary cost effectiveness analysis). Even if it is not found to be cost-saving, the economic analysis may show that use of ADM is relatively economically attractive. Furthermore, the primary aim of the RCT is to find a better method of breast reconstruction from the **patient perspective** in addition to the traditional assessments of outcomes such as complication rates and aesthetic results from a surgeon's perspective. This primary outcome will be measured using the Breast Q©**,** a prospectively designed and validated patient reported outcome questionnaire for breast reconstruction. Lastly, since the TE/I reconstructive method is performed routinely in community hospitals as well as teaching hospitals, research directed at improving implant reconstructive techniques has the potential to impact the most common practice in breast reconstruction and QOL of breast cancer survivors throughout North America.

iib. Innovation

This proposal for additional funding represents innovative work on three levels:

iib-1) One-stage ADM assisted implant reconstruction

Although multiple recent case series have demonstrated the feasibility of using Alloderm in immediate one-staged prosthetic breast reconstruction, this technique is still relatively novel and early in its practice. [12, 23-26] In addition, several authors have observed improved aesthetic outcomes with the use ADM in implant-based breast reconstruction.[12,23-26] Spear et al found that greater expansion in the lower breast pole can be achieved with the use of Alloderm.[12] He hypothesized that greater expansion in the lower pole allowed for the creation of a breast with greater ptosis and more natural breast contour. Breuing et al observed that the Alloderm sling created a sturdy, elastic sling that was strong enough to support the weight of the permanent implant preventing undue traction on the inferior mastectomy flap and at the same time reduced excessive upper-pole fullness.[23, 24] In addition, Salzberg observed in his large series of 76 immediate ADM-assisted breast reconstructions that visible implant rippling was prevented with the interposition of Alloderm even in patients with thin mastectomy skin flaps.[25]

iib- 2) Breast Q©

Traditional assessments of outcome in breast reconstruction have included an evaluation of complication rates and aesthetic results from a surgeon's perspective. Despite the recent emphasis on the importance of patient-reported outcome measurements, few instruments exist that are designed to accurately measure breast surgery outcomes from a patient's perspective. The recent development of the Breast Q©**,** a prospectively designed and validated patient reported outcome questionnaire for breast reconstruction has provided us with reliable information about the success of surgery from the patient's perspective. Using the Breast Q© as the primary outcome measure, this study aims to compare patient satisfaction between women receiving one-stage immediate breast reconstruction facilitated by ADM and those receiving the conventional two-stage TE/implant reconstruction without ADM. To date, there has been no prospective randomized trial comparing the efficacy, safety, aesthetic outcome, cost effectiveness, and most importantly patient-reported satisfaction between the ADM assisted one-stage reconstruction with the conventional two-stage reconstruction.

iib-3) Cost effectiveness analysis

Despite the importance of cost effectiveness analysis (CEA) in evaluating health outcomes and resource costs in surgical interventions, there is a paucity of this research in the area of post-mastectomy reconstruction.[14,27,28] Paramount in the CEA, is not only considerations of direct and indirect cost of intervention, but also patient perception of their health outcome (utility) and complications or morbidity as a consequence of the intervention. This sister analysis can be easily added to our current ongoing RCT, since we are already prospectively collecting information on both short- and long-term complications, patient satisfaction and QOL as part of the study protocol. In addition, we will add the EQ-5D QOL instrument that addresses 5 dimensions to evaluate the health status as reported by patients at the same time-points as the Breast Q©. Cost effectiveness analysis will be performed on **person-level** cost (direct and indirect) and effect data (Breast Q© global score and utility value on EQ-5D) using **net benefit regression**, a novel technique developed by our collaborator.(J.H.) [2-4,16-22] The cost data will come from hospital cost accounting systems and patient

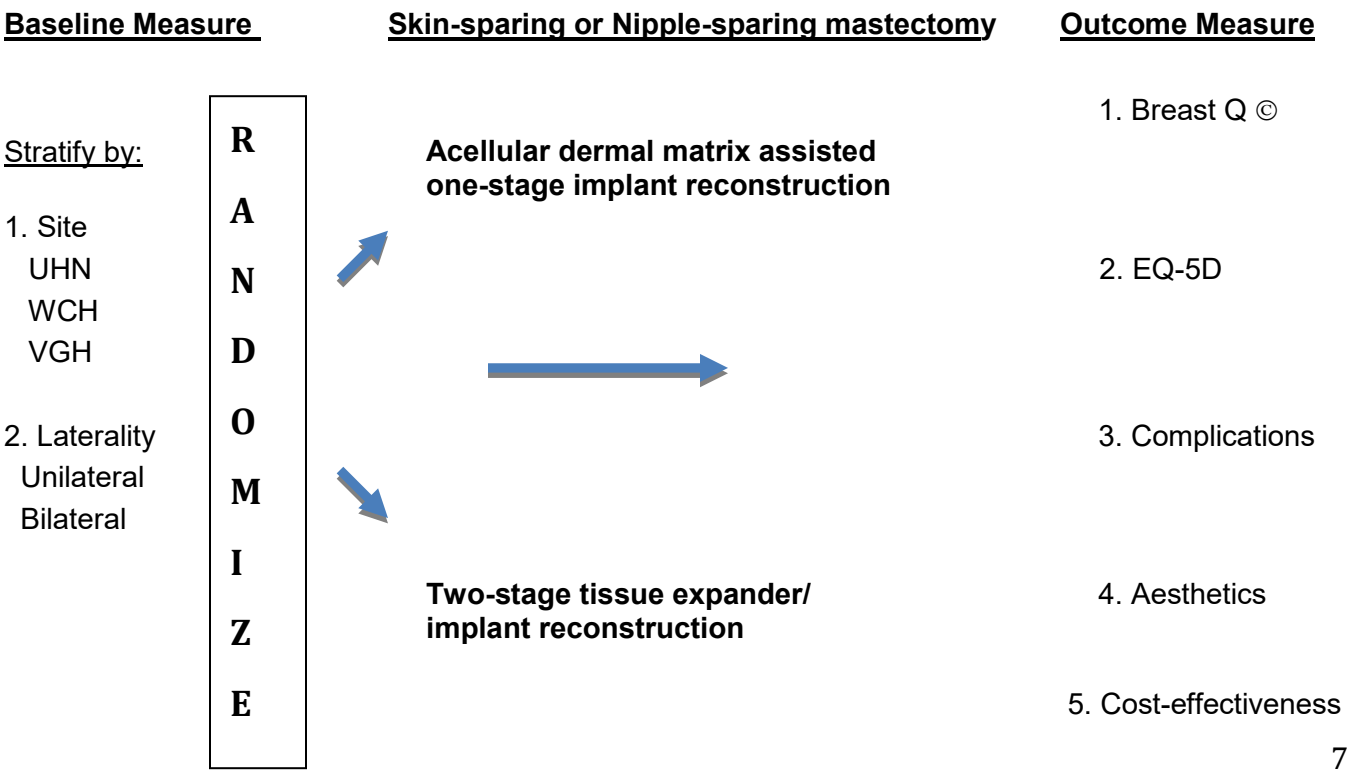
reports. Accurate case costing information is collected by the Accounting Department of the hospitals with each patient visit to the ambulatory clinic, emergency department, operating room, or in-patient ward. The primary patient outcome measure will be the global Breast Q© score and the secondary outcome measure will be quality adjusted life years (QALY) as measured by the EQ-5D. The versatility of the net benefit regressions is that it can be modeled for a variety of monetary values with the probability of cost-effectiveness plotted against values for money on a cost-effectiveness acceptability curve.[19] By eliminating the process of tissue expansion and a second operative procedure, we hypothesize that both the cost and utility as valued by patients will be superior in the 1-stage ADM method compared to the 2-stage TE/I method.

iic. Approach

iib-1. Study Design

This **multi-center randomized controlled trial** will evaluate the impact of implantable human cadaveric acellular dermal matrix in the setting of immediate one-stage implant breast reconstruction. Three separate sites will participate in the trial (University Health Network, Women's College Hospital, and Vancouver General Hospital). Institutional Research Ethic Board approval has been obtained for all three sites.(APPENDIX 2) After obtaining informed consent and confirming eligibility both pre- and intra-operatively, patients will be registered in the study. Patients will be enrolled until there are 72 evaluable patients enrolled in each study arm. Stratification will be performed based on the laterality of the reconstruction (unilateral vs. bilateral reconstruction) at each of the three study sites. Patients who are deemed eligible pre-operatively by the investigating surgeon for the study will be **randomized** to undergo either **one-stage permanent prosthetic placement** with the use of implantable **acellular dermal matrix** or the conventional **two-stage TE/implant procedure** without the tissue substitute.

Study Schema:



The **primary outcome** evaluated will be **patient-reported satisfaction and quality of life** associated with the use of ADM in one-stage immediate prosthetic breast reconstruction following skin-sparing or nipple-sparing mastectomy. Patient-reported satisfaction and quality of life will be measured using the Breast Q© questionnaire. These questionnaires will be administered to patients prior to mastectomy, at two weeks following the mastectomy and immediate reconstruction, 6 months and one year (+/- 1 month) following completion of reconstruction. It is hypothesized that ADM assisted one-stage prosthetic breast reconstruction will be associated with improvement in patient-reported satisfaction and quality of life compared to the conventional two-stage TE/implant reconstruction.

The **secondary outcomes** will include **short and long-term complication rates**, overall **aesthetic outcome** including capsular contracture formation at six month and one-year following completion of the reconstruction, and a **cost effectiveness analysis (CEA)**. For the cost-effectiveness analysis, person-level cost and effect data will be collected throughout the study. The cost data will come from hospital cost accounting systems and patient reports. The patient outcome data will be collected at months 6 and 12 months post-mastectomy by the Breast Q© and EQ-5D. The primary measure of effectiveness will be the global Breast Q © score and the secondary measure will be quality adjusted life years (QALY) as measured by the EQ-5D. It is hypothesized that the short- and long-term complication rates will be comparable between the two study arms, while the overall aesthetic outcome will be superior with less severe capsular contracture in the ADM assisted one-stage than the two-stage TE/implant reconstruction. Lastly, we hypothesize ADM assisted one-stage implant reconstruction will be the more cost effectiveness method of implant reconstruction following mastectomy than the standard two-stage TE/I method.

Timing of Questionnaires

Questionnaire	Baseline	**Mastectomy &**	2 weeks postop	6 months postop	12 months postop
Breast Q©	XX	**Immediate**	XX	XX	XX
EQ-5D	XX	**Breast Reconstruction**		XX	XX

iib-2. Patient Recruitment

Suitable participants will be identified by two Research Assistants (Toronto and Vancouver site) from the breast reconstruction clinics at the three study sites. All eligible participants will be accrued at the surgical centers to reach a target enrollment of 72 per arm. (Sample Size) Since our trial opened recruitment at the two study sites in Toronto in September 2009, a total of 67 women have been enrolled into the RCT. With the third site, Vancouver General Hospital joining the trial in January 2011, we anticipate that it would take until August 2011 to complete patient accrual.

iib-3. Eligibility

Eligibility will first be determined at the time of the pre-operative consult according to the inclusion/exclusion criteria outlined below:

Pre-operative eligibility:

Subject Inclusion Criteria

☐Patients who undergo immediate, implant-based reconstruction following skin-sparing mastectomy

☐Patients above the age of 18, no upper age limit
☐English-speaking

Subject Exclusion Criteria

☐Patient refusal
☐Patients with documented psychiatric history of psychosis or mental disorder excluding depression
☐Patients who are active smokers
☐Patients who will undergo any of the following:
☐Autologous tissue reconstruction
☐Combined implant and autologous tissue reconstruction
☐Patients with prior history of radiation or expected to receive post-operative radiation
☐Patients who are pregnant
☐Patients with grade III ptosis
☐Patients desiring final breast volume of greater than C cup

Following randomization preoperatively, eligibility will be determined once more intraoperatively:

Intra-operative eligibility:

Subject Inclusion Criteria

☐Patients who undergo sentinel lymph node biopsy without completion axillary lymph node dissection

Subject Exclusion Criteria

☐Patients who undergo therapeutic or completion axillary lymph node biopsy
☐Patients who have significant mastectomy flap ischemia or asymmetry between the two sides

If a completion or therapeutic axillary lymph node dissection is performed at the time of mastectomy, then the likelihood of the patient requiring postmastectomy radiation will be quite significant. It is anticipated that less than 5% of patients will be deemed ineligible on the basis of these 2 intra-operative exclusion criteria.

iib-4. Intervention plan

Pre-intervention Evaluation

During the pre-operative consultation, written informed consent will be obtained from patients who meet the inclusion and exclusion criteria and who are willing to participate. (APPENDIX 3)

Randomization

Randomization will occur in during the pre-operative consult although the participant's final eligibility will be determined during surgery (see section on Eligibility). Patients will be randomized to undergo either ADM assisted one-stage reconstruction or two-stage reconstruction with TE placement without the use of ADM. The randomization allocation list will be developed by the Department of Epidemiology and Biostatistics at the University Health Network Research Institute. Sequentially numbered and sealed envelopes containing the treatment assignments will be prepared and given to the study coordinator in charge of the study site. Each envelope will contain two identical datasheets with the patient's name, medical record number and treatment assignment. One sheet will be returned to the study coordinator and the other sheet will be placed in the patient's chart.

Group A: Experimental Treatment

In **Group A**, the experimental group, the plastic surgeon will create the breast pocket which will involve the use of an implantable layer of ADM. Pocket dissection will begin with elevation of the pectoralis major muscle. ADM will be used to create the infero-medial pocket thereby eliminating the need for surgical elevation of the anterior rectus fascia as well as the serratus musculature/fascia. It will be secured to the lateral border of the pectoralis major using absorbable sutures. Inferiorly, it will be sutured to the anterior rectus fascia along the base of the implant pocket. Laterally, it will be sutured to the serratus fascia in the line of the anterior axillary fold. A permanent anatomic cohesive silicone gel (Style 410, Allergan, Santa Barbara, CA) will be placed in the pocket and complete closure of the pocket will be performed using an absorbable suture. Two drains will be placed in the breast pocket, one deep to ADM and one on the superficial surface of ADM at the inferior mastectomy gutter.

Group B: Standard Treatment

In **Group B**, the standard treatment group, the tissue expander pocket will be made by elevating the pectoralis major muscle, serratus anterior muscle/fascia laterally and rectus fascia inferiorly. An anatomic-shaped tissue expander (Allergan, Santa Barbara, CA) will be placed beneath the muscle-fascial pocket and pocket will be closed using an absorbable suture. Sterile injectable saline will be used to inflate the tissue expander until an adequate volume without tension on the mastectomy skin flap is achieved. In this case, only one drain will be placed deep to the mastectomy skin flaps. All patients will receive standard peri-operative antibiotics.

iib-5. Interventional agent

ADM derived from cadaveric human skin tissue is supplied by US AATB-compliant tissue banks utilizing the standards of the American Association of Tissue Banks (AATB) and Food and Drug Administration's (FDA) guidelines. We will use Alloderm (6 x 12cm) labeled “Thick”. We have no financial or other conflicts of interest to report for LifeCell corporation. The tissue substitute will be stored under refrigeration at 1°C -10°C (34-50°F) as recommended by the product insert. Alloderm will be opened and placed on the operating room table in a sterile fashion, and soaked in sterile water for a minimum of 20 minutes before implantation.

iib-6. Postoperative treatment

In **Group B**, at 2 weeks after the operation, office expansion will be undertaken and continued on a biweekly basis. With each expansion, the endpoint of expansion will include either: (1) persistent blanching or congestion of the mastectomy flap; or, (2) patient discomfort. The expansion phase will be considered complete once the volume in the expanded breast represents 100 percent (+/- 20 percent) of the recommended expander volume. If required, postoperative chemotherapy is generally given during the expansion period. Expanders are then exchanged approximately between 4-6 weeks following the completion of chemotherapy or 3-6 months following completion of inflation. All patients in group B will undergo a second exchange procedure at which time the expander is removed and a permanent implant is placed. In all instances, the permanent implant to be used will be anatomic cohesive silicone gel implants (Style 410, Allergan, Santa Barbara, CA).

iib-7. Confounders and their Measurements

Critical covariates will be identified at baseline and documented in the demographic assessment forms. These confounders can be conceptually divided into procedure specific, patient specific, and disease specific confounders. Analysis will be adjusted for the confounders using both stratification and multivariate regression. (see section on Outcome and their measurements) Stratified randomization is

performed based on laterality of the reconstruction (unilateral vs. bilateral) and study site. Other procedure specific confounders include skin-sparing vs. nipple-sparing mastectomy and the primary reconstructive surgeon. The patient specific confounders will include age, body mass index; socioeconomic status assessed using proxy measures of income and highest obtained level of education and marital status. Co-morbidities will be categorized as having one or more the following possible chronic conditions (emphysema, heart disease, diabetes, hypertension, stroke, arthritis, or other chronic condition). The disease specific confounders will include stage of breast cancer and present or past chemotherapy treatment.

iib-8. Outcomes and their measurements

Primary Outcome: ***Patient-Reported Satisfaction and Quality of Life***

Patient satisfaction and quality of life will be measured using the Breast Q© as a self-administered questionnaire. The Breast Q© has 2 subscales that examine the two different domains: satisfaction and psychosocial function. [9, 29]The scores generated for each subscale will be transformed on a scale from 0-100, lowest to highest summary scores respectively. Scale validity and reliability are supported by the high Cronbach's alpha coefficient (>0.80) and intra-class correlation coefficients (>0.70). The scores generated for each subscale will be transformed on a scale from 0-100, lowest to highest summary scores respectively. Participants will be asked to complete the pre-operative module of the Breast Q© questionnaire at 2 weeks prior to the mastectomy.(APPENDIX 4) Post-operatively, they will be requested to complete the post-operative module of the Breast Q© at 2 weeks following immediate reconstruction, as well as 6 months and 1 year following the completion of the reconstruction. (APPENDIX 5) The questionnaires will be self-administered and mailed to the participants with return envelopes and prepaid postage. To compensate our study patients for their participation, a monetary reimbursement ($10) will be available upon completion. The Dillman method will be used to encourage patient response.[30]

The **secondary outcomes** will include a comparison of:

1. **short and long-term complication rates**: Short-term complications are intra- and post-operative complications occurring within two months of surgery and long-term complications occur later than two-months. They will be documented and collected prospectively.

2. **long-term aesthetic result:** Evaluation of the overall aesthetic result and capsular contracture grade will be performed at six months and one year following the completion of reconstruction. A routine physical examination will be performed by the attending surgeon and photographic documentation (5 standardized photographs) of the reconstruction will be obtained at the six month and one-year follow-up visit. A panel of three independent, blinded observers will subsequently evaluate the overall aesthetic result using the three-point, five item, Breast Aesthetic Score described by Lowery with the use of photographic documentation. [31,32]Capsular contracture will be graded by the examining physician and will be graded using the Modified Baker Scale for Reconstructed Breasts, which is widely accepted to be the gold-standard measure of capsular contracture grade.[33]

3. **cost-effectiveness**: Costs and effects will be simultaneously analyzed by collecting person-level cost and effect data. The cost data will come from hospital cost accounting systems and patient reports. The patient outcome data will be collected at months 6 and 12 months post-mastectomy by Breast Q©

and EQ-5D. The frequently used generic HRQol instrument EQ-5D will be piggy-backed to the Breast Q© at the 2 post-mastectomy time-points to generate a utility value for current health. The primary measure of effectiveness will be the Breast Q score and the secondary measure will be quality adjusted life years (QALY) as measured by the EQ-5D[34,35] (APPENDIX 6)

iib-9. Data Analysis

9a. Confounders and their Measurements

Critical covariates will be identified at baseline and documented in the demographic assessment forms. (APPENDIX 7) Analysis will be adjusted for the confounders using both stratification and controlled for during repeated measures analysis using SPSS v18.

Stratification

Stratified randomization will be performed based on two a priori factors that can influence outcome: unilateral vs. bilateral reconstruction, and study site. (Study Schema diagram) It is well documented in the literature that aesthetic outcomes tend to be superior in bilateral reconstructions than unilateral cases.[36, 37] In addition, patients will be stratified by the study site as there may be significant differences in patient characteristics for each individual hospital catchment area.

9b. Intention to treat analysis

Patients who abandon reconstruction or undergo premature explanation of either TE or implant will ***not*** be removed from the study and will be evaluated using the **intention-to-treat analysis**.

9c. Measurement of the Primary Objective:

i) Primary Analysis

Each of the two domain-specific summary scores on function and satisfaction will be transformed on a scale from 0 to 100 using RUMM software. Mean scores and standard deviation for each surgery group will be calculated and compared. To address our primary aim of comparing patient satisfaction and quality of life between **Group 1** (one-stage with ADM) and **Group 2** (two-stage group without ADM) before and at the three post mastectomy follow up reference time points, we will use the **repeated measure analysis** to examine the time effect and time-group interaction. In all analyses, statistical significance will be designated at $p <= 0.05$ level.

ii) Secondary Analysis

Short-term (intra-operative and early post-operative) and long-term postoperative complications will be documented and collected prospectively at each site by the study coordinator. Group comparisons will be performed using the Pearson's chi-square test or binomial test, where appropriate for these categorical variables. Repeated measure analysis will be used for Breast Aesthetic Score at 6 and 12 months post mastectomy. The Modified Baker Scale for capsular contracture results in an ordinal variable which will be compared using the Pearson's chi-square test.

iii) Cost-effectiveness analysis

CEA on person-level cost and effect data will be conducted using net benefit (nb) regression described by our collaborator (J.H.).[2] This technique allows CEA to be conducted using traditional

regression methods. The dependent variable for the net benefit regression in this analysis will be nb which equals effect $\times$ $ - cost where effect = primary outcome of IIRS, $ = the monetary value of each unit of effect and cost = the costs accrued over the study period. As noted above, the data for effect and for cost will be collected as part of the study's comparison of the two reconstructive methods. Different values of $ will be used to see how sensitive the results are to assumptions about $. In the base case scenario, the dependent variable nb will be modeled as a function of an indicator variable (TX=0 if in the two-stage TE/I group and TX=1 if in the one-stage ADM assisted group) and potentially confounding variables. We shall estimate the coefficient β_{TX} in the regression nb = β_0 + β_x **X** + β_{TX} TX + ε where **X** is a vector of potentially confounding variables, β_x is a vector of their respective coefficient estimates, ε is a stochastic error term, TX is the new treatment indicator and β_{TX} is an estimate of the incremental net benefit. When $\beta_{TX} > 0$, the intervention is deemed to be cost-effective since the value of the extra benefit is greater than the extra cost. Net benefit regressions will be repeated for a variety of $ values and then the probability of cost-effectiveness will be plotted against values for $ on a cost-effectiveness acceptability curve. In this way, the research findings will allow different decision makers to use different preferred values of $. By placing the CEA in a regression framework, we will then be able to use a wide variety of regression tools, for example, those to identify key subgroups for hypothesis generation and model diagnostic tools.

iib-10. Sample Size

We consider clinically relevant change in the quality of life as a difference that exceeds half a standard deviation of the baseline value. Field-testing data of the Breast Q© has found that the standard deviation of both the psychosocial function and satisfaction distributions is approximately 20. Thus, the minimum significant difference of score in each subscale is calculated to be 10. When we set our power at 85% with a β error of 0.1 and a standard α error rate of 0.05, and applied the equation for equal sample sizes, we calculated a **minimum sample size of 72 patients per arm** for a total sample size of 144 patients. This sample size is also sufficient with power 84%, α 0.05, to detect a value of 0.06 for η2, representing a medium effect size of the proportion of variability in the outcome variable (Breast Q©) that is explained by the independent variable(s), e.g., intervention.

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