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A randomised controlled trial comparing the use of Alloderm versus Dermacell in immediate implant based breast reconstruction (REaCT-ADM)

Coordinating Centre: The Ottawa Hospital Cancer Centre

Principal Investigator: Angel Arnaout, MD
The Ottawa Hospital Cancer Centre
E-mail: anarnaout@toh.ca

Co-Principal Investigators: Drs. E. Cordeiro (Breast Surgeon), J Zhang (Plastic Surgeon), A. Ghumman (Plastic Surgeon)

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PROTOCOL SIGNATURE PAGE

My signature below confirms that I have reviewed and approved this protocol, and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and all applicable local regulations

_____

Qualified Investigator (Please Print)

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Qualified Investigator Signature

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Date

November 24, 2016

1. Background:

Breast reconstruction after mastectomy has been shown to provide psychosocial benefits to breast cancer patients and is considered an integral part of breast cancer treatment [1]. In general, breast reconstruction can be accomplished using the patient's own tissues (autologous), or implantable prosthetic devices (alloplastic reconstruction or breast implants). Over the last decade, there has been a significant increase in the rate of alloplastic reconstructions compared with autologous tissue reconstructions in North America [1-3].

Acellular dermal matrix (ADM) has been increasingly used in alloplastic reconstruction. ADMs are biological materials, typically of human, bovine, or porcine origin [3-6]. The tissue is processed to remove cells as well as any antigenic component to prevent immune reaction, resulting in a residual collagen matrix or scaffold that facilitates tissue ingrowth and revascularization by the host following implantation. Originally described for the use in resurfacing of burn injuries and abdominal wall repair; ADMs are now commonly used in the field of implant-based breast reconstruction post mastectomy (Figure 1). The advantages of ADM-assisted implant reconstruction is that it provides additional tissue coverage and helps in the positioning of the implant while minimizing peri-prosthetic fibrosis (i.e. capsular contracture) [6-8], the latter being especially important for patients who receive adjuvant radiation as part of their breast cancer treatment [9]. Whereas traditional implant-based breast reconstruction occurs in a "delayed" fashion, performed at least 6 months post mastectomy; the use of ADMs have allowed conversion in the appropriate patient to a single stage, "immediate" breast reconstruction (done at the same operative procedure as the mastectomy) [3-6].

The significant impact on reduced operative procedures for the patient [6-9], psychological benefit from having restoration of the breast immediately post mastectomy (i.e. direct to implant breast reconstruction) [10-11], cost savings from sparing a second surgery [12-15] as well as improved aesthetic outcomes (compared to non-ADM assisted breast implant reconstruction) [16-17] has made the ADM-assisted approach to become a standard of care at many centers and widely adopted throughout the world [18-21]. Currently at the Ottawa Hospital, a cursory audit in 2015 demonstrated that approximately 50% of the 800 breast cancer patients underwent a mastectomy; 25% of these underwent immediate breast reconstruction for which ADM is used (i.e. around 100 breast cases per year).

Patients who undergo direct-to-implant breast reconstruction with ADMs have been found to experience similar rates of postoperative complications compared with patients who undergo two-stage reconstruction without ADMs, and therefore this procedure is generally considered to be a safe and reliable approach to breast reconstruction [18-23]. A summary of the evidence on outcomes after direct-to-implant breast reconstruction using ADMs is presented in Table 1. Overall, direct-to-implant reconstruction outcomes compare favourably with the Mentor and Allergan Core Study results, which tracked complications and revision rates following delayed two-stage implant reconstruction without ADM (24,25). On short-term follow-up, weighted analysis of the studies in Table 1 shows direct-to-implant reconstruction with ADM to have lower rates of capsular contracture comapred to two-stage reconstruction without ADM (0.3% versus 8.3% to 17.1%), seroma (1.2% versus 4.9%), infection (1.4% versus 3.2% to 5.7%), late revision (8.5% versus 27% to 53.3%) and implant loss (1.5% versus 5.7% to 7.7%). Higher rates of mastectomy flap necrosis in immediate reconstruction with ADM (4.7% versus 2.3%) may be

related to increased tension placed on the skin closure with immediate placement of the permanent prosthesis.

Various ADMs are offered on the market and the costs vary widely despite very similar qualities. The two most commonly used ADM products in North America by far are Dermacell and Alloderm [2-4,32]. The difference between the two products include a) the level of sterility , with Dermacell being sterilized to 10^{-9} while Alloderm is sterilized to 10^{-6} and b) the consistency and thickness of the biologic material and c) a significant difference in cost (standard 6x16cm piece of Dermacell = $2200 CAD and Alloderm = $3600 CAD). For a typical patient, the difference in cost for the hospital is about $1400. Supporters of Dermacell advocate for its lower cost and increased sterility; whether the difference in sterility translates into a clinical difference in infection rate is unclear (standard procedure is to sterilize to 10^{-6} for operative devices) [32-36]. Supporters of Alloderm advocate based on its longer term data on safety and effectiveness (2-4,19,32] as it is the ADM that has been around the longest. Each product has shown to be safe and effective (32-26). As such there exists clinical equipoise. Currently, the selection of ADM is based on non-clinical idiosyncratic decision making factors, such as the hospital's previous relationship with the vendors and preference of the surgeon. Both products are equally available to Canadian hospitals and currently at the Ottawa Hospital the product used is dependent on surgeon preference.

1.1 The REaCT Program

New cancer treatments are developed through occurrence of randomized clinical trials (RCTs), comparing with either a placebo or an established treatment. Pharmaceutical company funded

trials establish the new treatments as being; better, worse or more commonly equivalent to established therapies. As a result, in clinical practice, physicians may be faced with multiple funded “standards of care”. However, comparative standard of care treatment trials are rarely conducted. One of the major barriers is expense. It is incredibly expensive to perform clinical trials as their regulatory oversight (patient consent, REB submission, contracts, drug costs, research coordination and management, data collection of multiple often superfluous endpoints, analysis) has been designed around trials of new agents or established agents for new indications.

As physicians do not know what the “best” treatment for patients is, genuine uncertainty (“clinical equipoise”) exists. In the light of different strategies chosen by investigators between those two trials aforementioned, physicians will choose between different “standards” in their personal practice, using idiosyncratic decision making processes, without the physician or the patient knowing the optimal option. Determining the optimal treatment remains an important medical issue for both patients and physicians.

This study will use an established methodology to allow comparisons of established standard of care treatment using the “integrated consent model” as part of a pragmatic clinical trial. By integrating medical and clinical practices, physicians will be able to inform their patients about the RCT, through a typical conversation between the physician and patient, without written informed consent. This clinical interaction would then be documented, as ordinarily done in practice.

Pragmatic clinical trials are being given increased importance, as they commonly consist of comparative effectiveness research, thus comparing the safety and effectiveness of diagnostic, therapeutic or delivery systems. Additionally, these studies have not only the ability to leverage patient data from electronic health records to increase sample size of trials at much lower costs,

but also enabling major national and international initiatives to generate the data needed to improve care. As such, the Integrated Consent Model is being increasingly used internationally to improve patient care. In fact, the Ottawa Hospital Cancer Centre is leading this program with over 150 patients already enrolled on REACT trials at four Canadian Cancer Centres (Ottawa, Kingston, Edmonton, Kitchener). These studies have shown excellent patient feedback with 97% of patients rating being 'completely satisfied' with the REACT process.

Thus, we propose a pragmatic clinical trial to evaluate Alloderm with Dermacell in a head to head randomized fashion, with regards to the postoperative complications, namely infection, seroma formation (as measure by drain duration and output), loss of the implant, incidence of revisional surgery and capsular contracture. These postoperative sequelae have significant implications to the patient, surgeon and health care system. The most significant of these are postoperative infection, which can result in prolonged antibiotic use, hospital admission, loss of implant, and delay in adjuvant breast cancer therapy.

2. Study Aim

The aim of this study is to evaluate the postsurgical complications of Alloderm versus Dermacell use in immediate breast reconstruction.

3. Hypothesis

We predict that Dermacell will have reduced postoperative comlications as compared to Alloderm due to its improved sterility.

4. Consent Process

Patients will be asked to provide oral consent to be randomized to once either Alloderm or Dermacell. In this study the investigator will obtain oral consent using the attached REB approved consent script.

If the patient agrees to participate in the study, then the surgeon will dictate in the progress note they have had the above type of conversation with the patient. There will be no need for the patient to sign an informed consent form. The patient will be given a written summary of the general information about the study as well.

4. Study Design

In this randomized superiority trial, the site investigator will have the on-line program uploaded to their health authority secured computer in clinic or electronic portable device (e.g. smartphone) in order to randomize participants. The surgeon must dictate that the verbal consent and eligibility review has taken place prior to randomization.

Inclusion Criteria:

- Female patient
- Ages 20-90

- All patients undergoing mastectomy for breast cancer or prophylaxis for breast cancer with immediate implant-based reconstruction
- Able to provide verbal consent

Exclusion Criteria:

- Patients who have had prior chest wall or irradiation on the reconstructed side
- Patients not undergoing immediate breast reconstruction at the time of mastectomy
- Any patient with a contraindication to immediate breast reconstruction

It should be noted that patients who undergo bilateral mastectomy and bilateral immediate implant reconstruction should be randomized to the same type of ADM for each breast ie the randomization is at the patient level and not the breast level. Patients having bilateral mastectomy will have each breast evaluated separately, as 2 entries the final results database. Both breasts of the same patient will receive the same randomization arm.

A history of smoking, BMI > 40, and D cup breast size or grade III ptosis are all contraindications to immediate breast reconstruction as the risk of postoperative complications are significantly higher (wound infection, dehiscence, implant loss, seroma) than the average patient and thus these patients would be excluded from the study.

5. Outcomes

Primary outcome: Postoperative duration of drain placement (days)

Secondary outcomes: All outcomes are measured within 6 months of the initial surgery

- Episodes of seroma formation requiring aspiration

- Loss of implant
- Revisional surgery/ return to operating room
- Wound dehiscence or debridement
- Capsular contracture (as identified by the plastic surgeon)
- Number of additional postoperative clinic visits with the plastic surgeon (beyond the routine)
- Economic impact will be assessed based on calculation of total costs with each material used to include the material costs, duration of operative room use, clinic and inpatient hospital costs, surgical billing costs and anaesthesia costs

6. Study Procedures

All patients undergoing mastectomy for breast cancer or breast cancer prophylaxis are seen at the WBHC at the Ottawa Hospital. Patients eligible and consenting for for immediate breast reconstruction with an implant will be introduced to the REACT-ADM study and a standardized verbal consent for randomization will be recorded in the clinic notes. The clinical research assistant (CRA) will be performing the randomization and will inform the surgeon on the day of surgery with regards to the randomization arm immediately before the surgery. Both Dermacell and Alloderm will be readily available in the operating room for use in case of randomization into either arm.

The plastic surgeon will be informed of the randomization arm and will proceed with the surgery in the usual fashion, with standard, equivalent procedures used for both (aseptic technique, drainsplacement, oral antibiotics for 1 week postoperatively). The routine schedule of postoperative follow-up of these patients is as follows:

Breast Surgeon:

- 2 weeks
- 6 months

Plastic Surgeon:

- 1 weeks
- 2 weeks
- 6 months

7. Sample size calculation and Data Analysis Plan

The primary endpoint of the study is drain duration (days). Mean postoperative duration of drain placement is 10 days. As per informal discussion with the plastic and breast surgeons, a minimum of 4 days in drain duration between the 2 arms will be considered clinically significant. We are hypothesizing that there will be minimum of 4 day difference in drain duration, in favour of Dermacell as this is a superiority trial. As such, we will require 50 patients total (25 per arm) to demonstrate a 4 day difference in drainage duration (14 vs 10) with a standard deviation of 5. Allowing for a 105 study drop out rate, we will require a total of 56 pts or 23 patients per arm. The Ottawa Hospital currently performs 100 immediate breast reconstructions per year with ADM. As such, the study duration would be expected to be 1 years. Data will be analysed at the end of the year.

The primary endpoint of the study is drain duration (days). We will compare mean postoperative duration of drain placement between both arms by calculating the post-randomization absolute mean difference in durations and its 95% confidence interval. We will also present the associated two-sample t-statistic. If data are not normally distributed, we will compare groups using a Mann-Whitney test. Our dichotomous secondary outcomes (episodes of seroma formation requiring aspiration, loss of implant, revisional surgery/ return to operating room, wound dehiscence or debridement, capsular contracture (as identified by the plastic surgeon) will be analyzed be calculating relative risk ratios and their 95% confidence intervals. Our continuous outcome (number of additional postoperative clinic visits with the plastic surgeon beyond the routine) will be analyzed using parametric (t-statistic) or non-parametric (Mann-Whitney) tests depending on distribution of occurrences. Patients having bilateral mastectomy will have each breast evaluated separately, as 2 entries the final results database. Both breasts of the same patient will receive the same randomization arm.

8. Data Collection

Once the patient has been randomized, the study CRA will collect participant information via electronic health records. From a study standpoint only the CRA will access this information. Data not available at the time of visit will be collected from the dictated physician/surgeon note. At the time of randomization the software will also generate a reminder email to the patient's physician to collect study related data. Patients having bilateral mastectomy will have each breast evaluated separately, as 2 entries the final results database. However, both breasts of the same patient will receive the same randomization arm.

9. Risks

There are no incremental risks associated with this study as both arms are standard of care treatments.

10. Premature withdrawl

Participants have the right to withdraw from the study treatment at any time for any reason.

Investigator has the right and obligation to withdraw subjects from the study treatment in the event of:

- Intercurrent illnesses which would, in the judgment of the investigator, affect assessment of clinical status to a significant degree, and require discontinuation of protocol therapy
- Any toxicity that would produce further harm if continued on the protocol
- Request by the participant or of their legally authorized representative (consent withdrawal)
- Non-compliance to the study protocol or logistic consideration
- Participant is lost to follow-up

11.Monitoring

This study will be conducted according to the International Conference on Harmonisation Good Clinical Practice Guidelines. Routine quality assurance will be completed by the Ottawa Hospital Research Institute and its delegates to ensure that the study is being run according to the protocol at the participating site. This monitoring will include:

- random spot checks on inclusion and exclusion criteria to confirm that only eligible patients are participating in the trial
- routine evaluation of source data to ensure accuracy
- evaluation of the first set of case report forms from each site to ensure that they are being completed according to the protocol.

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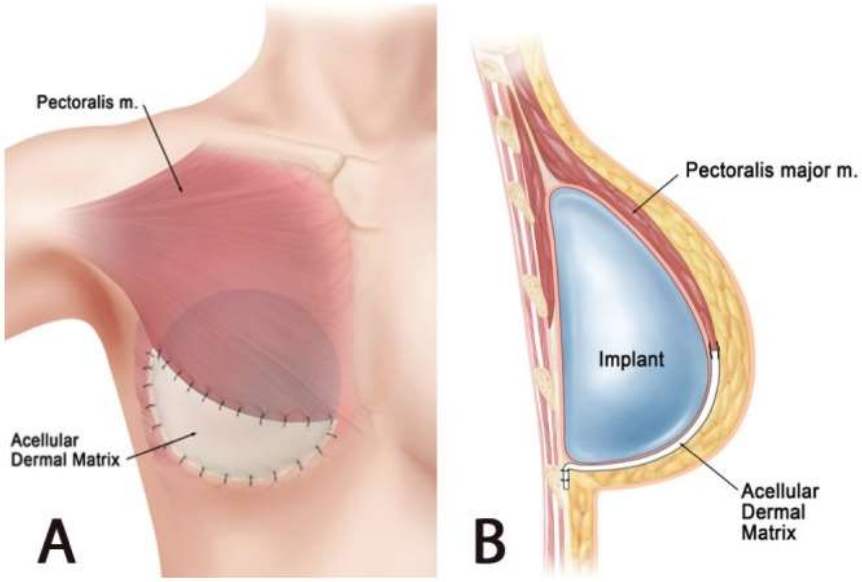

A *Acellular dermal matrix coverage of implant (anteroposterior).* **B** *Acellular dermal matrix coverage of implant (lateral). m Muscle*

Figure 1: Illustration of role of acellular dermal matrix in implant based reconstruction.

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Table 1

Use of acellular dermal matrices in direct-to-implant breast reconstructive surgery

Author (reference), country	Title	Acellular dermal matrix	Sample	Follow-up	Mastectomy flap necrosis requiring revision, %	Capsular contracture rate, %	Late revision rate, %	Seroma rate, %	Infection rate, %	Implant extrusion or requirement for autologous salvage, %
Ashikari et al (24), USA	Subcutaneous mastectomy and immediate reconstruction for prevention of breast cancer for high-risk patients	AlloDerm®* 4 cm × 12 cm	65 patients, 130 breasts One stage	4.6 years ± 56 months	N/D	N/D	N/D	N/D	0	N/D
Austen et al (25), USA	A simplified technique for single stage breast reconstruction	AlloDerm® 4 cm × 12 cm 4 cm × 16 cm	25 patients, 35 breasts One stage	10 months	5.7 (2 cases revised in office setting)	N/D	8.6 (1 implant exchanged for asymmetry, one for rippling)	N/D	N/D	2.9
Breuing et al (11), USA	Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings	AlloDerm® 4–6 cm × 14–16 cm	10 patients, 20 breasts One stage	6 months to 1 year	5 (Revised in office setting)	0	0	0	0	0
Colwell et al (26), USA	Retrospective review of 331 consecutive immediate single stage implant reconstructions with acellular dermal matrix: Indications, complications, trends and costs	AlloDerm®	211 patients, 331 breasts One stage	N/D	9.1	N/D	N/D	1.5	3.0	1.5
Gamboa-Bobadilla (27), USA	Implant breast reconstruction using acellular dermal matrix	AlloDerm® 4 cm × 16 cm	11 patients, 13 breasts One stage	14 months	N/D	N/D	N/D	7.7	7.7	7.7
Salzberg et al (28), USA	An 8-year experience of direct-to-implant immediate breast reconstruction using human acellular dermal matrix (AlloDerm)	AlloDerm®	260 patients, 466 breasts One stage	28.9±21.3 months	1.1	0.4 Both cases (2) required operative intervention	9.4 (Most frequent revision was to increase implant size)	N/D	0.2	1.3
Salzberg et al (29), USA	Nonexpansive immediate breast reconstruction using human acellular tissue matrix graft (AlloDerm)	AlloDerm®	49 patients, 76 breasts One stage	18 months (range 3–52 months)	3.9 (2 managed conservatively with dressings, one managed operatively)	0	N/D	0	0	0
Topol et al (30), USA	Immediate single-stage breast reconstruction using implants and human acellular dermal tissue matrix with adjustment of the lower pole of the breast to reduce unwanted lift	AlloDerm® 4 cm × 16 cm	23 patients, 35 breasts One stage	9.5 months (range 1–24 months)	0	0	N/D	0	8.6	5.7
Zienowicz and Karacaoglu (31), USA	Implant-based breast reconstruction with allograft	AlloDerm®	24 patients, 30 breasts One stage with adjustable implant	18 months (range 15–24 months)	20 (All managed conservatively)	0	0	0	0	0
Overall weighted average by breast (one stage)†					4.7 (47/993)	0.3 (2/627)	8.5 (47/551)	1.2 (6/505)	1.4 (15/1101)	1.5 (15/1006)
Allergan‡ Core Study for Primary Reconstruction (24) (7-year follow-up; n=98)					2.3	17.1	53.3	N/D	3.2	7.7
Mentor§ Core Study for Primary Reconstruction (25) (3-year follow-up; n=251)					N/D	8.3	27	4.9	5.7	5.7

Note: weighted averages calculated by breast.

*LifeCell Corporation, USA;

†Studies with a mix of one- and two-stage reconstructions, or studies that did not report results by breast not included in weighted average;

‡Allergan Inc, USA; §Mentor Worldwide LLC, USA. N/D Not documented