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| protocol |
| Patient-controlled needle-free carbon dioxide insufflated breast expander implant (Aeroform®, AirXpanders®) in breast reconstruction: multi-surgeon prospective case series |
| Version Number: 1  Date: 13/01/18 |
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STATEMENT OF COMPLIANCE

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC *National Statement on Ethical Conduct in Human Research (2007) – Updated May 2015*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95)*.

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Add Anna, Dilip and Mark…

**STUDY SYNOPSIS**

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| Title: | Patient-controlled needle-free carbon dioxide insufflated breast expander implant (Aeroform®, AirXpander®) in breast reconstruction: multi-surgeon prospective case series |
| Short Title: | Air expander trial |
| Study sites where project will take place: | GCHHS (Robina Hospital and GCUH) |
| Study Objectives: | To establish the safety and efficacy of patient-controlled needle-free carbon dioxide insufflated breast expander implants (Aeroform®, AirXpanders®) in a high volume multi-surgeon unit. |
| Study Design: | Prospective consecutive case series (Phase 2 trial) |
| Study Outcome Measures: | Safety- device related events, breast related events, other adverse events  Efficacy- device success, time to completion of expansion, time to second stage procedure |
| Study Population: | Inclusion criteria:  1) participant requires immediate or delayed breast reconstruction using expander implant  2) participant is over the age of 18  Exclusion criteria:  1) participant is unable to give informed consent |
| Number of participants: | 50 |
| Translation to Changes in Clinical Practice: | See Appendix 1 |
| Key Ethical and Safety considerations: | There may be a perceived unequal or dependent relationship between the treating surgeon and potential participants. This will be addressed by the first approach about the trial being made by the Breast Care Nurse or the Bond MD student assigned to this project.  Potential participants may also be highly dependent on medical care if they are undergoing reconstruction for cancer, especially in the immediate setting. It will be specifically stated in the PICF that the usual medical care of the potential participant will not be affected by their participation or non-participation in the trial.  There are potential harms to any surgical procedures; the existing literature and Australian single-surgeon series suggests that these are not likely to be higher that the existing comparator (surgeon-controlled saline-expanded implant) |

a. Glossary of Abbreviations, Terms, and Acronyms

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| **Abbreviation, Term, Acronym** | **Definition (using lay language)** |
| GCHHS | Gold Coast Hospital and Health Service |
| GCUH | Gold Coast University Hospital |
| MD | Medical Doctorate |
| PI | Principal investigator |
| PICF | Patient information and consent form |
| UR | Unit Record |

b. Background

A two-stage tissue expander–to-implant procedure is the most common implant-based reconstructive method, and accounted for 2868 procedures in Australia in 2016.1 The saline implant with self-sealing port was patented in 1980 by Radovan2 and requires serial bolus injections of saline to be administered by a clinician every few weeks after surgery. This process can be uncomfortable, lengthy, and logistically challenging for patients and clinics due to the need for ongoing recurrent appointments.3

The AeroForm® tissue expander (AirXpanders® Inc., Palo Alto, California) is a remote-controlled, carbon dioxide–filled breast tissue expander. It was designed to provide women with a gradual, needle-free, controlled, and faster method of completing the expansion process. This system is composed of an implantable tissue expander containing a reservoir of compressed carbon dioxide, and an external hand-held remote control. The patient uses the controller to activate a valve within the reservoir to release carbon dioxide into the expander, eliminating the necessity for repeated injections and the associated clinic visits. The device is programmed to allow patient dosing in increments of 10 cm3. Multiple safety mechanisms are incorporated into the device design; only one 10cm3 dose of carbon dioxide may be administered during a 3-hour period, and no more than three doses (30 cm3) of carbon dioxide may be given per day.

The AeroForm® expander demonstrated successful expansion within 2 weeks with no adverse effects in a sheep model,4 and the first human trials, conducted in Australia, demonstrated 100 percent success rates in the Patient-Activated Controlled Expansion I and II (pilot and extended pilot) trials.5,6 These were single-surgeon trials. These early trials, supported with additional data from the Australian Aspirin to Prevent Recurrent Venous Thromboembolism trial,7 provided the basis for successful Therapeutic Goods Administration approval of the device in Australia.

The only randomised, controlled trial, AeroForm® Patient Activated controlled tissue expander (XPAND) has been performed in the United States, showing statistically significant shorter expansion and reconstruction times compared to saline implant, non-inferiority for safety with a 10 percent margin, and high rates of patient-rated ease, convenience, and satisfaction.8

The purpose of this study is to undertake the first multi-surgeon case series in Australia. AeroForm® is already standard supply in Gold Coast Health, with very positive patient feedback about the convenience and comfort of patient-controlled inflation. However, it is very important to the surgeons of the unit that clinical outcomes are also satisfactory.

Importantly, this trial is intended to be inclusive, reflecting real-world patients in a high volume breast unit. The inclusion and exclusion criteria have been kept to a minimum, in contrast to previously published trials which have often been restricted to populations which form a minority of our actual patients by excluding cancer indications, BMI >33, smokers, diabetics and so on. This may result in a wider range of treatment outcomes than previously published trials, but it is hoped that the information arising from this study will also be more realistic and applicable to the settings of other breast units around Australasia.

c. Study objective

To establish the safety and efficacy of patient-controlled needle-free carbon dioxide insufflated breast expander implants (Aeroform®, AirXpanders®) in a high volume multi-surgeon unit.

d. Methods

a. Study design

Prospective, consecutive case series

b. Study setting

Recruitment, surgery, data collection and data analysis will be carried out at Robina Hospital and GCUH.

c. Study population

Inclusion criteria:

1) participant requires immediate or delayed breast reconstruction using expander implant

2) participant is over the age of 18

Exclusion criteria:

1) participant is unable to give informed consent

d. Study recruitment

Potential participants will be identified at the time of booking for breast reconstruction using expander implant, after completing the operative consent process. Potential participants will be approached by the Breast Care Nurse (who sees breast surgical patients routinely in the Breast clinic) or the Bond MD student assigned to this project (who will be ‘shadowing’ the Breast Care Nurse). Potential participants will be provided with a patient information and consent sheet to consider.

e. Consent

Potential participants who wish to take part in the trial can return their completed consent form to the Breast Care Nurse or Bond MD student, at the surgical planning, preassessment or anaesthetic clinics. These occur 1-2 weeks prior to scheduled surgery, usually 2-3 weeks after the initial consultation.

f. Participant confidentiality

Once recruited, participants will be identified by UR number and date of birth on a password-protected study spreadsheet held securely behind the QHealth firewall. Names will not be kept. Patients will be re-identified only for the purpose of collecting follow-up data via the electronic medical record. From data analysis onwards, data will be de-identified by using aggregated data (mean, median, standard deviation etc.) or by using the sequential numbering on the study spreadsheet for description of individual cases. Publication will predominantly involve aggregated de-identified data, and any individual data (eg discussion of individual or outlier cases) will only be identified using the allocated spreadsheet number.

g. Participant safety

The PICF provides details for the local breast care nurse and Cancer Psychology services for participants who may require additional support.

h. Participant withdrawal from the study

Participants will be able to withdraw from the study at any time by advising any of the PIs verbally, by email, or by returning the withdrawal of consent form. Any data collected from participants who withdraw will be erased.

i. Study procedure

The PIs will meet four weeks prior to the start of recruitment. Team meetings continue fortnightly to review progress will until the completion of the study.

Participants will be enrolled prospectively. Each participant will undergo AeroForm® insertion under existing clinical quality measures, and involvement in the trial will not alter the usual clinical management in any way.

Clinical data will be collected as below.

j. Study outcomes

Safety will be assessed through adverse events collected through the electronic medical record, and double-checked against events presented at the monthly unit morbidity and mortality meeting.

Efficacy will be assessed by device success (device integrity in-situ until second-stage procedure), number of days from first procedure to completion of expansion, and number of days from first procedure to second-stage procedure.

k. Data collection

Data will be held in a study-specific database on the coordinating investigator’s computer within Queensland Health electronic security protections, and will be additionally protected by password. It will be backed up onto a password-protected USB. Hard copy forms will be held in a locked office at Robina Hospital. The database will be ‘locked’ to further alterations (made read-only) after the completion of data entry. The database will be maintained for 5 years and then destroyed.

l. Data analysis

Quantitative data (number of days) will be analysed with descriptive statistics. These will include measures of central tendency (mean, median, mode) and spread (standard deviation). Individual adverse effects and device success/failure will be described qualitatively.

m. Translation to changes in clinical practice

As this is the first research performed in GCHHS in this topic area, it is difficult to anticipate the exact nature of potential benefits. An indicative list is included in Appendix 1.

n. Timeline

First PI meeting by Monday 1st April, 2019

Participant recruitment opens Monday 29th April, 2019

Participant recruitment closes at 50 participants ~ April 2020

Data analysis complete by June 2020

Begin publication writeup August 2019

e. Funding

Resources for the study will be provided in-kind from the respective services.

f. References

1. Australian Breast Device Registry: 2016 Report. Monash University, March 2018. https://www.abdr.org.au/wp-content/uploads/2018/04/2016-ABDR-Report-web-uploaded.pdf

2. Radovan C, Schulte RR, inventors; Heyer-Schulte Corp, assignee. Flap development device and method of progressively increasing skin area. United States patent US 4,217,889. 1980 Aug 19.

3. Finlayson CA, MacDermott TA, Arya J. Can specific preoperative counselling increase the likelihood a woman will choose postmastectomy breast reconstruction? Am J Surg. 2001;182:649–653.

4. Jacobs DI, Jones CS, Menard RM. CO2-based tissue expansion: A study of initial performance in ovine subjects. Aesthet Surg J. 2012;32:103–109

5. Connell AF. Patient-activated controlled expansion for breast reconstruction with controlled carbon dioxide inflation: A feasibility study. Plast Reconstr Surg. 2011;128:848–852

6. Connell AF. Patient-activated controlled expansion for breast reconstruction using controlled carbon dioxide inflation: Confirmation of a feasibility study. Plast Reconstr Surg. 2014;134:503e–511e

7. Connell TF. Results from the ASPIRE study for breast reconstruction utilizing the AeroForm patient controlled carbon dioxide-inflated tissue expanders. J Plast Reconstr Aesthet Surg. 2015;68:1255–1261

8. Ascherman JA, Zeidler K, Morrison KA, Appel JZ, Berkowitz RL, Castle J, Colwell A, Chun Y, Johnson D, Mohebali K. Carbon dioxide–based versus saline tissue expansion for breast reconstruction: results of the XPAND prospective, randomized clinical trial. Plastic and reconstructive surgery. 2016 Dec 1;138(6):1161-70.

**Appendix 1.**

**Translation of Study Outcomes to Changes in Clinical Practice.**

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| **Change in Clinical Practice** | **Example** |
| Knowledge of Practitioners | GCHHS surgeons will know whether Aeroform® implants are sufficiently safe and effective for routine use. |
| More applied clinical research or quality improvement activity | Identified areas for improvement such as Aeroform®-specific complications or training requirements will lead to further research and quality improvement projects. |
| Clinical Process | Routine use of Aeroform® will free up clinic time previously required for clinician-initiated saline expansion. This efficiency will create more clinical capacity, for example to shorten the waiting time for new referrals. |
| Unit expertise and recognition | GCHHS surgeons will be gain expertise in a new technology. This will increase recognition of the unit through being able to disseminate knowledge to colleagues in other units through publications and conference presentations. |