Capsular Contracture in Breast Reconstruction

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Contents

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Glossary

ADM…….. Acellular dermal matrix
α-SMA……..... Alpha-smooth muscle actin
ACAN……Aggrecan
BRCA1…….. Breast cancer 1
BRI……. Bradford Royal Infirmary
COL1A1…….Collagen type I
COL3A1……. Collagen type III
CTGF……. Connective tissue growth factor
DMEM…… Dulbecco's modified eagle's medium
EDTA……. Ethylenediaminetetraacetic acid
FBS…… Fetal bovine serum
FDA…… Food and Drug Administration
HADM…… Human acellular dermal matrix
HRA…… Health research authority
HSP-60……..Heat shock protein 60
IL8…….. Interleukin 8
IL10…… Interleukin 10
MMP12…….. Matrix metalloproteinase 12
MROC…… Mastectomy reconstruction outcomes consortium
MTA……Material transfer agreement
NMBRA……. National Mastectomy and Breast Reconstruction Audit
PBS…… phosphate buffered saline
PDGF……Platelet derived growth factor
PROMs……..Patient reported outcome measures
RCT……Randomised controlled trial
RVI……. Royal Victoria Infirmary
RW……. Rebecca Wilson, Lead Researcher
SAA1……..Serum amyloid A1
SEM……Standard error of mean
TE……Tissue expander
TGF-β1…….. Transforming growth factor beta 1
TIMP4…… Tissue inhibitor of metalloproteinase 4
TNFα……. Tumour necrosis factor alpha
TNFSF11…….. Tumour necrosis factor superfamily member 11
UHSM…… University Hospital of South Manchester

Abstract

Introduction: In the UK, more than 55000 women are diagnosed with breast cancer each year. There has been a 50% increase in the number of women undergoing immediate breast reconstruction after mastectomy, greater than 85% of these are implant based. One of the most common and unpredictable long-term complications is capsular contracture, occurring in up to 25% of cases. Acellular dermal matrices (ADM), now commonly used in immediate reconstruction, have been associated with reduced rates of capsular contracture but evidence supporting this is limited.

Aims: In patients undergoing immediate implant based breast reconstruction with either Strattice™ or a submuscular technique, to determine and compare i) the incidence of capsular contracture and rates of revision surgery ii) patient reported outcomes iii) cosmetic outcomes and iv) short-term clinical outcomes. In vitro, to compare the implant capsule at the ADM interface and the native tissue (pectoralis muscle) interface.

Methods: A retrospective multicentre cohort study of patients who underwent immediate implant based reconstruction with Strattice™ or a submuscular technique between January 2009 and December 2015 across three tertiary UK centres. Clinical examination and tonometry was performed, medical photographs and a comprehensive case note review undertaken. Participants completed the BREAST-Q. In patients undergoing revision surgery after immediate implant based sub pectoral Strattice™ reconstruction biopsies were taken from two different areas of the capsule (ADM tissue interface versus pectoral tissue interface) and analysed using histology and immunohistochemistry.

Results: The outcomes for 553 Strattice™ reconstructions and 242 submuscular reconstructions were compared. Unplanned explantation rate as a complication of primary surgery was 8.5% in the Strattice™-assisted group compared to 5.4% in the submuscular. Revision rates were equivalent between the groups (46.7% vs. 41.1%) but there were less revisions performed in the Strattice™-assisted group for capsular contracture (5.3% vs. 15.6%, p=<0.001). Capsular contracture occurred in 13.5% of the Strattice™ reconstructions compared to 21.5% of the submuscular (p=0.14). There were significantly higher aesthetic satisfaction scores from all three independent assessors in the Strattice™ group. There was no difference in BREAST-Q scores between the two groups.

Capsules from 12 reconstructions were analysed at a median time of 6 months (range 5 – 81.5 months) from the last procedure. No difference in severity of inflammation between the two capsules was demonstrated but a difference in location of inflammation and an absence of the inner synovial like metaplasia layer in the ADM capsule was seen. The percentage of myofibroblasts was greater in the ADM capsules (p=0.04). In capsules older than two years there was higher proportion of elastin in the native capsule (p=0.0086). There was a greater proportion of mature collagen in the ADM capsules older than six months (p=NS).

Conclusion: Strattice™ reduces capsular contracture whilst improving aesthetic outcomes in implant based breast reconstruction. ADMs may reduce capsular contracture by creating a barrier between the native tissues and implant, leading to a less intense foreign body response which remains dormant over time.

Declarations

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List of presentations

Oral Presentations

Long-term outcomes in ADM-assisted breast reconstruction compared to a submuscular technique – the results of the BROWSE multicentre cohort study
Rebecca L Wilson, Cliona C Kirwan, Joseph M O'Donoghue, Richard A Linforth, Richard K Johnson, James R Harvey – MBN Milan Breast Meeting 2019 (Invited)

Implants and soft tissue interaction: do ADMS act as a barrier?
Rebecca L Wilson, Rebecca McKerrell, Susan Pritchard, Cliona C Kirwan, James R Harvey, Ardeshir Bayat – MBN Milan Breast Meeting 2019 (Invited)

Breast reconstruction with and without Strattice™ – a prospective multicentre study
Rebecca L Wilson, Cliona C Kirwan, Joseph M O'Donoghue, Richard A Linforth, Richard K Johnson, James R Harvey – Moynihan Chirurgical Club research prize session 2019

Can Strattice™ reduce the long-term incidence of capsular contracture compared to a submuscular implant based breast reconstruction? – a prospective multicentre study
Rebecca L Wilson, Katie Stocking, Cliona C Kirwan, Joseph M O'Donoghue, Richard A Linforth, Richard K Johnson, James R Harvey - Association of Breast Surgeons 2019

How expensive is immediate autologous breast reconstruction? A long-term cost comparison with implant-based reconstruction
Nicholas Pantelides, Rebecca Teasdale, David Pearson, James Harvey, Jonathan Duncan – British Association of Plastic Reconstructive and Aesthetic Surgeons 2017

Effect of ADM-assisted breast reconstruction on reducing the need for long-term (five year) revisional surgery compared to a submuscular technique
Rebecca L Wilson, Cliona C Kirwan, Joseph M O'Donoghue, Richard A Linforth, Richard K Johnson, James R Harvey - Association of Breast Surgeons 2017

Poster Presentations

The long-term outcomes of the BROWSE multicentre cohort study comparing Strattice™-assisted implant based reconstruction and submuscular reconstruction
Rebecca L Wilson, Cliona C Kirwan, Joseph M O'Donoghue, Richard A Linforth, Richard K Johnson, James R Harvey - San Antonio Breast Cancer Symposium 2018

One stage ADM-assisted breast reconstruction, as safe as two stage submuscular implant breast reconstruction

Rebecca L Wilson, Cliona C Kirwan, Joseph M O'Donoghue, Richard A Linforth, Richard K Johnson, James R Harvey - Association of Breast Surgeons 2017

Long term risk of explantation with Strattice™ based breast reconstruction, is it any different to submuscular reconstruction?

Rebecca L Wilson, Cliona C Kirwan, Richard K Johnson, James R Harvey - San Antonio Breast Cancer Symposium 2016

1. Introduction

1.1 Breast Cancer

1.1.1 Epidemiology

In the UK more than 55,000 women are diagnosed with breast cancer each year, making it the most common cancer in women and currently the most common cancer in the UK (1). Annually there are approximately 11,500 deaths from breast cancer in the UK (1). Worldwide breast cancer is the second most common cancer after lung but the most common in women with an estimated 1.68 million cases diagnosed in 2012 (2). However more than 80% of women are still alive five years from their diagnosis. With such a high survival rate, ensuring quality of life in survivorship is critical.

1.1.2 Surgical Management

Breast conserving surgery

Breast conserving surgery is the removal of the cancer with a margin of healthy tissue around it, and thus leaving behind the majority of the breast. Whether this is possible depends on the location, type and size of the cancer and breast. Large randomised controlled trials demonstrated no difference in survival for those who had breast conserving surgery with whole breast radiation compared to mastectomy alone for tumours up to 5cm (3-5). Breast conserving surgery can be done independently (wide local excision) or in combination with plastic surgical techniques to improve cosmetic outcome (6). However, there are many instances where breast conserving surgery may not be appropriate or feasible.

Mastectomy

A mastectomy is the surgical removal of all breast tissue. It is performed for cancers not amenable to breast conserving surgery, in patients unable to have radiotherapy or for patients who may be suitable for breast conserving surgery but would prefer to have the whole breast removed. After breast conserving surgery, approximately 9% proceed to mastectomy due to positive surgical margins (7). Large, central, multifocal cancers are relative indications for mastectomy, along with recurrent cancers in women previously treated with breast radiotherapy. A mastectomy can be performed using a number of techniques, removing varying amounts of skin with or without the nipple areolar complex depending on the location of the cancer, body habitus and breast shape of the patient and plans for reconstruction.

Mastectomies are also performed for risk reduction in those deemed high risk of developing cancer in the future. There has been an increase in publicity of hereditary breast cancer following Angelina Jolie's revelation that she underwent bilateral risk reducing mastectomy as a carrier of the BRAC1 gene mutation. This has seen a sustained two-fold increase in requests for gene testing and subsequent referrals for risk reducing surgery in the UK (8), which is often accompanied by breast reconstruction.

1.2 Breast Reconstruction

Breast reconstruction is surgery to recreate the breast mound. The broad methods of breast reconstruction include autologous where the patient's own tissue is taken from a different area of their body, implant-based or a combination of both. The aim of reconstruction is to recreate the most symmetrical, natural looking breast shape possible, in a safe, acceptable way for the individual patient. Doing so can improve their physical and psychological well-being (9-12). The national mastectomy and breast reconstruction audit comparing patient reported outcomes in mastectomy alone (n=4726) and breast reconstruction (n=2384) using the BREAST-Q reported higher levels of emotional and sexual well-being in those undergoing breast reconstruction (12).

1.2.1 Autologous breast reconstruction

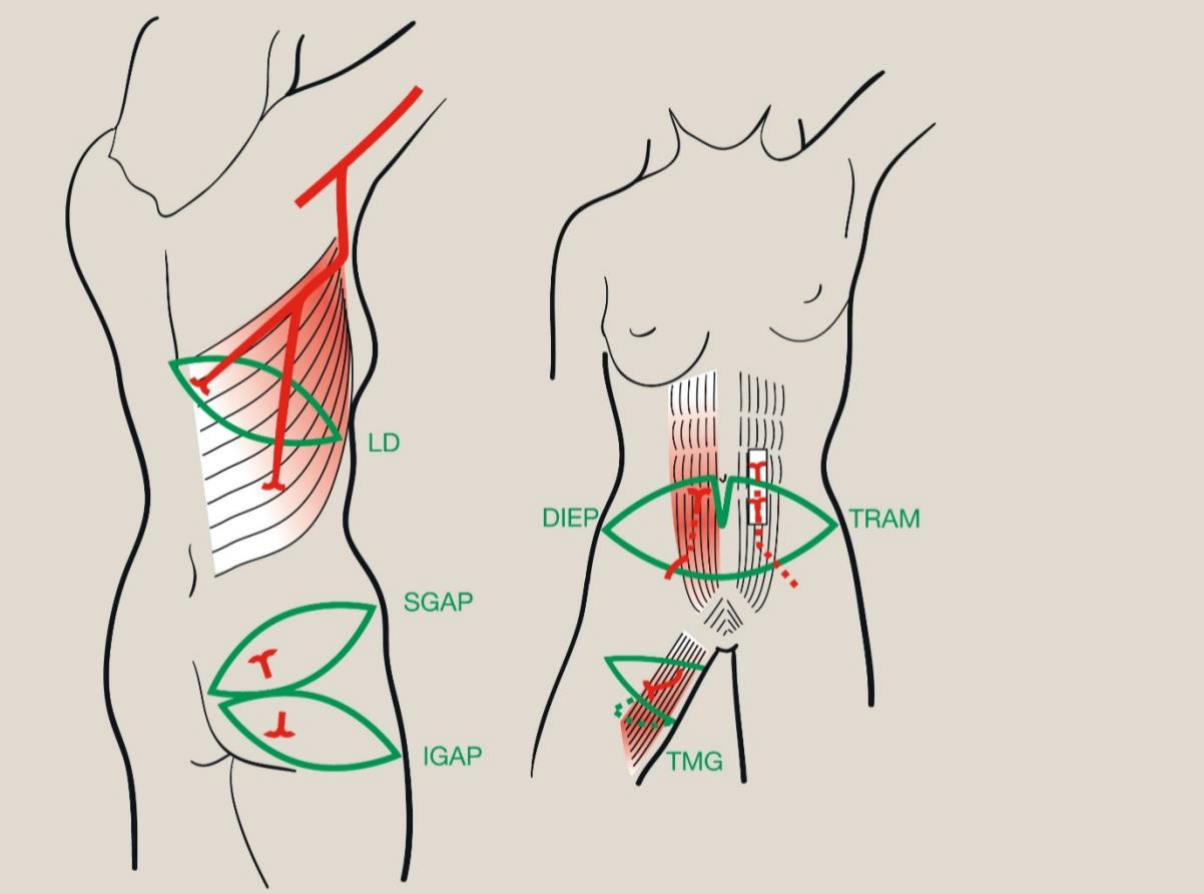
Autologous reconstruction is when the patient's own muscle and tissues are used to recreate the breast mound. This can be attached to the original blood supply, pedicle flap or detached from the original blood supply and new anastomosis formed, free flap.

History of autologous reconstruction

The first autologous muscle flap, using latissimus dorsi, was described by Iginio Tasini in 1896 (13). He experienced consistent necrosis of the distal third of the flap and continued to revise it over the next decade. Contralateral breast and abdominal tube flaps were performed but abandoned due to poor outcomes with high donor site morbidity. In the early 1900s the only successful technique with acceptable aesthetic outcomes was the Holdsworth four-stage tube flap. However reconstruction was not widely accepted until the mid-1900s because of concerns that "reconstruction might conceal tumour recurrence and increase the chances of tumour dissemination" (14). The Holdsworth flap was replaced by the latissimus dorsi myocutaneous flap after it was re-popularised in 1976 now including the overlying skin (15). With many modifications over the following decades, including dividing the skin bridge, isolating the vascular pedicle and dividing the thoracodorsal nerve (16-18), it remains a current technique in breast reconstruction. Other successful techniques followed which are still used today, including the transverse rectus abdominus myocutaneous (TRAM) flap first described in 1982 (19) and deep inferior epigastric perforator (DIEP) flap in 1994 (20).

Current techniques in autologous reconstruction

Current techniques in autologous reconstructions include the pedicle latissimus dorsi flap where the flap of skin, fat and muscle is rotated from the back onto the chest wall. Free flaps are taken from the abdomen, buttocks and thighs (deep inferior epigastric perforator, superior/inferior gluteal artery perforator, and transverse musculocutaneous gracilis) (Figure 1). There are advantages to autologous reconstruction (Table 1), however there is a current decline in numbers performed (21).



LD, latissimus dorsi; SGAP, superior gluteal artery perforator; IGAP, inferior gluteal artery perforator; DIEP, deep inferior epigastric perforator; TMG, transverse myocutaneous gracilis; TRAM, transverse rectus abdominis myocutaneous.

Figure 1 Diagrammatic representation of common pedicle and free flaps. Reproduced with permission from Critchley et al. (2016); Surgical techniques in breast cancer: an overview. Breast (22)

Advantages and disadvantages of autologous reconstruction

Table 1 Advantages and disadvantages of autologous reconstruction

Advantages	Disadvantages
• More natural appearance • Change with increase/decrease in body weight • Avoid implant associated complications • More tolerable of radiotherapy • Less revision surgery	• Longer operating time • Longer hospital stay • Longer recovery time • Donor site morbidity • Muscle weakness • More scarring i.e. at donor site

1.2.2 Implant-based reconstruction

Implant-based reconstruction uses a manufactured prosthetic to provide the volume to rebuild the breast mound. Currently these are made of silicone, saline or a combination of both with a smooth, textured or polyurethane coating.

History of implant-based reconstruction

Attempts at prosthetic reconstruction were made using paraffin injections in 1889 (23) then polyvinylic sponge implants (24) however severe complications arose from the major foreign body reaction and both techniques were abandoned. The first "implant" inserted was an autologous lipoma in 1895. After 6 months the neo-breast remained viable (25). In the early 1900's several other items were implanted such as glass and ivory balls, with little success. Thomas Cronin suggested filling a sac with silicone after seeing a blood bag hanging up that resembled the shape of a breast. After successfully experimenting in dogs, silicone implants were successfully implanted in humans in 1962, both for cosmetic augmentation and breast reconstruction (25, 26). Initial subcutaneous implant positioning was associated with skin flap necrosis, explant migration and exposure and was largely replaced by submuscular coverage (27). Improvements in implant manufacturing continued, changing the shell and filling, making it now the most common type of breast reconstruction performed. In 2012 85% of immediate breast reconstructions performed were implant based (21).

Current techniques in implant-based breast reconstruction

Implant-based techniques are i) single-staged procedures, where a fixed volume implant or adjustable permanent expander e.g. Becker™ implant is inserted or ii) two-staged procedures where a tissue expander is used. The traditional two-staged technique involves raising pectoralis major with or without serratus anterior to create either a complete or partial submuscular pocket to insert the tissue expander in to (27). The tissue expander is gradually expanded via an internal or external subcutaneous port, over a number of weeks until the desired volume is achieved and replaced with a fixed volume implant (Figure 2). This technique is associated with loss of lower pole projection and infra-mammary fold definition because of reduced stretch of the pocket.

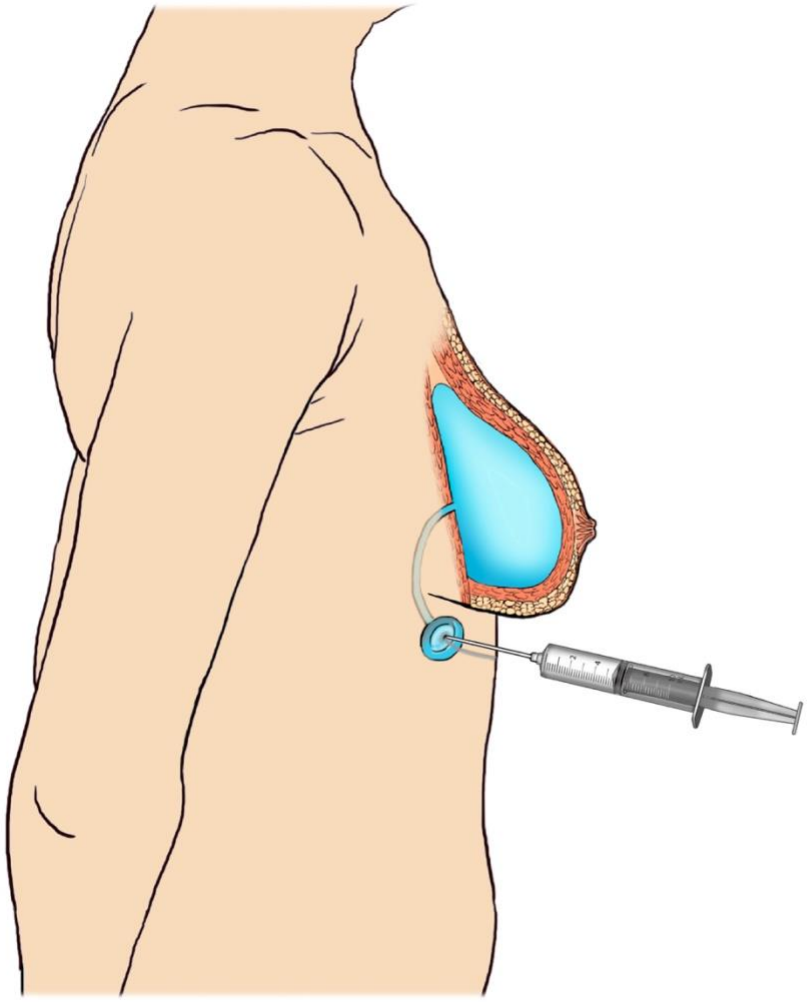


Figure 2 Two-stage total submuscular breast reconstruction with tissue expander after nipple sparing mastectomy (authors own image, created by Helen Carruthers, Medical Illustration, MFT)

Adaptations of the traditional technique evolved to give lower pole coverage using a dermal sling (28-30) or acellular dermal matrix (ADM)/synthetic mesh (31) (Figure 3), allowing for either a single-staged or two-staged procedure to be performed. Dermal slings are derived from de-epithelializing the lower mastectomy flap and are particularly advantageous in women with ptotic breasts. ADM technique is more advantageous in smaller, non-ptotic breasted women.

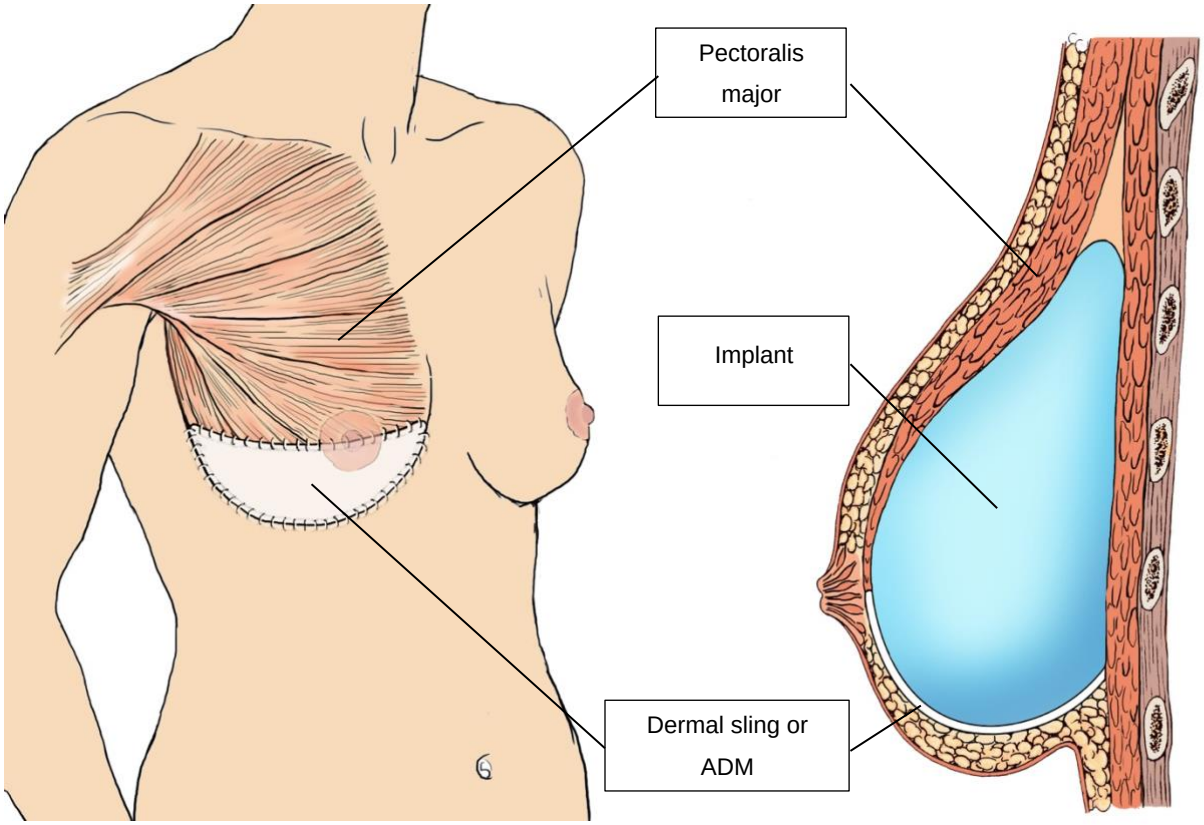


Figure 3 Single-stage (direct to implant) immediate breast reconstruction using ADM or dermal sling after nipple sparing mastectomy. Showing ADM sutured between the detached lower border of pectoralis and chest wall at inframammary fold or dermal sling from its original attachment at the inframammary fold and sutured to the detached lower border of pectoralis to create a lower-pole sling, to support and cover the implant (authors own image, created by Helen Carruthers, Medical Illustration, MFT)

The elevation of pectoralis major for upper pole coverage can be associated with functional impairment and breast animation. This has led to prepectoral total ADM coverage or upper pole ADM coverage and lower pole dermal flap (Figure 4) (32, 33). Short –term post-operative outcomes are comparable with subpectoral-ADM technique (34-36). Inpatient pain scores are reduced with prepectoral function and full range of shoulder motion is returned in half the time of that with subpectoral-ADM reconstructions (37). Aesthetic outcome (patient and physician assessed) was found to be excellent in 58.5% (117/200) and good in 31.5% (63/200) after a mean follow-up of 36 months (range 3 – 68 months) and no animation or Grade III/IV capsular contracture was observed (38).

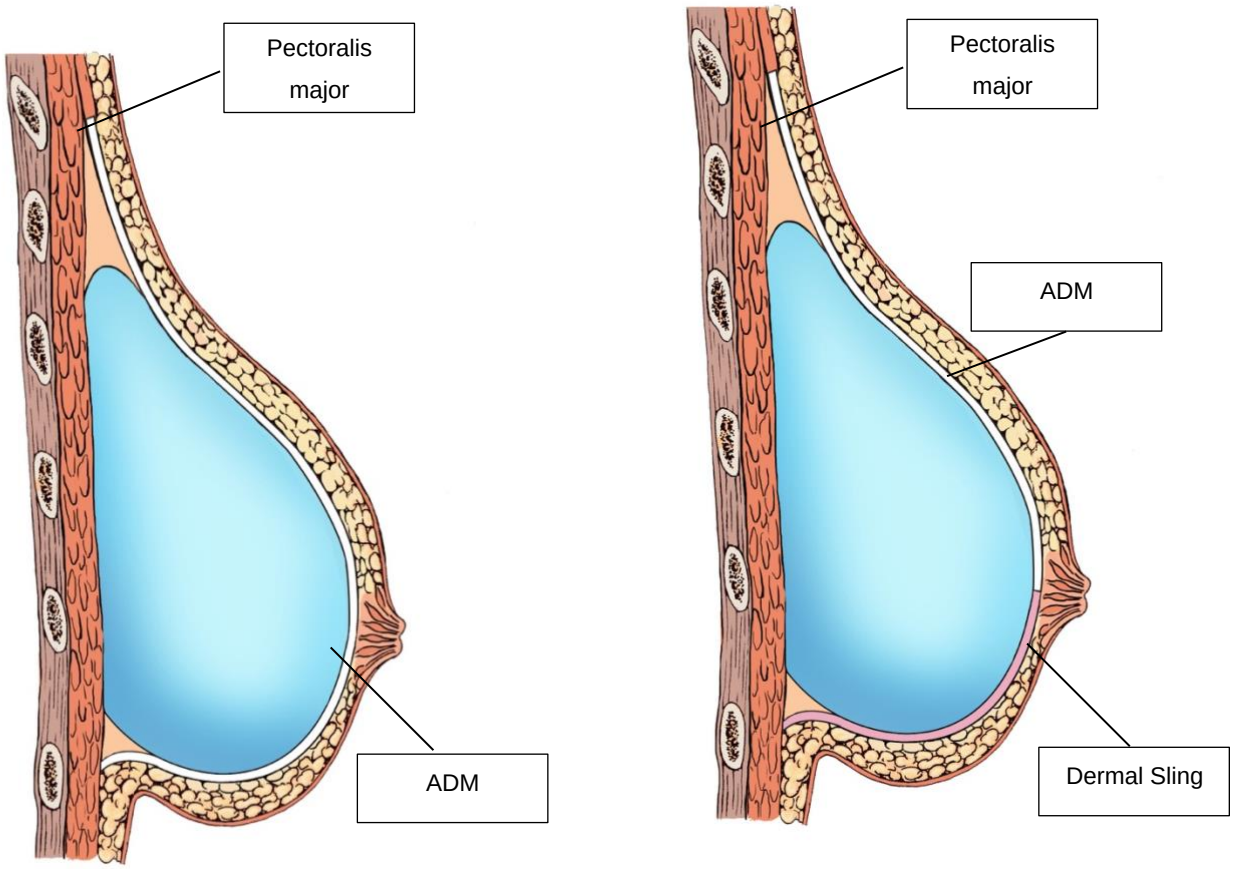


Figure 4 Left: Single-stage (direct to implant) immediate breast reconstruction using prepectoral total cover ADM after nipple sparing mastectomy showing the ADM sutured to the chest wall in the upper and lower border of the breast. Right: Single-stage (direct to implant) immediate breast reconstruction using prepectoral upper pole ADM coverage sutured to a lower pole dermal sling after nipple sparing mastectomy (authors own image, created by Helen Carruthers, Medical Illustration, MFT)

Indications for and contraindications to implant-based reconstruction

Implants sit pert on the chest wall, with little movement. It is an ideal form of reconstruction for patients with small, minimally ptotic breasts, as the shape provided by implant based reconstruction is a closer match to this type of breast. Patient preference is the leading factor in the choice of reconstructive procedure however it may be influenced by the surgeon's preference and the treating unit's capabilities. Other relative indications and contraindications to an implant based procedure are: patient factors; body habitus, skin and soft tissues are only able to support a maximum volume and original/contralateral breast size may exceed this, hence autologous reconstruction may be more appropriate to give the extra volume. Conversely, in a slim patient, autologous donor sites may be insufficient to provide the required volume. Patient lifestyle may preclude an autologous form of reconstruction for example a rock climber who does not want to reduce shoulder function due to a latissimus dorsi flap reconstruction (39, 40). Significant co-morbidities contraindicate the longer operating time and morbidity associated with an autologous reconstruction. A review of 14,585 implant based reconstructions demonstrated age greater than 55 years (Odds ratio [OR] 1.66, p=0.013), obesity (OR 3.17, p<0.001) and active smoking (OR 2.95, p<0.001) are factors associated with higher failure rates in immediate implant based reconstruction (41).

In the same cohort, obesity was also associated with higher rates of post-operative infection (OR 1.6, p<0.001), delayed wound healing (OR 2.1, p<0.001) and return to theatre (OR 1.6, p<0.001) (42) and diabetes higher rates of infection (OR 17.46, p=<0.001) (43). Previous or adjuvant radiotherapy is a main factor when considering implant based reconstruction as it can significantly increase implant loss, capsular contracture rates and effect aesthetic outcome (44, 45).

Advantages of implant-based breast reconstruction

Implant based breast reconstruction offers the advantage of a shorter procedure with a quicker recovery time, due to the lack of harvesting of an autologous flap. Other benefits include less scarring and no donor site morbidity or consequences of losing tissue such as muscle weakness.

Disadvantages of implant-based breast reconstruction

In implant-based breast reconstruction the implant sits pert on the chest wall with very little movement and can feel cold and firm giving a less natural breast. Disadvantages associated with complications of the implant itself are explantation, capsular contracture, rupture, malposition, rippling and animation (46, 47). With an estimated risk of 1 in 24,000 per breast implant, breast implant associated anaplastic large cell lymphoma is a rare but recognised sequela (48). There have been approximately 600 cases reported worldwide resulting in 33 deaths (49). Implants do not change as natural tissues do leading to progressive asymmetry as the contralateral breast ages or if there is significant weight gain or loss, resulting in rates of revision surgery as high as 81% at 10 years (46), to achieve acceptable results.

Radiotherapy pre and post implant-based breast reconstruction

Radiotherapy increased implant based reconstruction failure rates from 6% (22/386) to 25% (16/64) and 15% (45/304) in patients who had previous or adjuvant radiotherapy, respectively (p<0.001) (50). In the same multi-centre cohort study of 754 breasts previous and adjuvant radiotherapy significantly increased the re-operation rate (44% vs. 66% vs. 59%). Similarly, adjuvant radiotherapy (n=319) in a study of 2133 implant based reconstruction found increased implant loss rates (0.5% vs. 9.1%, p<0.01) and increased rates of grade IV capsular contracture (0.5% vs. 6.9%, p<0.01)(44). Patient satisfaction is lower in all aspects of the BREAST-Q after radiotherapy (219/633 patients)(51).

1.2.3 Immediate versus delayed breast reconstruction

Breast reconstruction can be performed at the time of mastectomy (immediate) or at a separate time point in the future (delayed); both have advantages and disadvantages (Table 2). A recent meta-analysis of seven studies (3756 patients) demonstrated an increased risk of surgical site infection in immediate breast reconstruction compared to mastectomy alone (RR 1.51, p=0.0001). A prospective study comparing immediate (n=209) and delayed (n=116) reconstructions found a higher total complication rate in the immediate group (52% vs. 33%, p<0.001) (52). Relative contraindications, predominantly factors that would put a patient at an increased risk of complications with a reconstructive procedure compared to an oncological procedure alone, are smoking, obesity, multiple co-morbidities, previous breast irradiation, need for axillary node clearance or adjuvant therapy and inflammatory breast cancer (22).

A retrospective study of 184 patients (270 reconstructions, 71 axillary node clearances) after adjusting for other risk factors demonstrated patients undergoing reconstruction with axillary node clearance are more prone to a major complication (OR 3.49, 95% CI, 1.4-8.5; $p<0.01$) (53). In a survey of 557 Canadian surgeons and oncologists, 35% felt immediate breast reconstruction delayed adjuvant therapy (54). A systematic review failed to find a relationship between immediate breast reconstruction and delay to adjuvant treatment; however of the 14 studies included many were small, retrospective, single centre studies (55). Results of the iBRA-2 study, a prospective multicentre cohort study (n=2631) have shown immediate breast reconstruction does not impact the time to delivery of adjuvant therapy (56). Increase numbers of immediate reconstruction are now being performed (12, 21) and this will be the focus of the current research project.

Table 2 Advantages and disadvantages of immediate and delayed breast reconstruction (22)

	Advantages	**Disadvantages**
Immediate breast reconstruction	Patient does not experience psycho-social effect of simple mastectomy alone Potentially single procedure Preserve skin envelope ± nipple Avoid need for tissue expansion Cost-effective	Risk of complications - May delay adjuvant treatment - Psychological blow if expectations not met Further adjustment surgery often needed Considerable time pressure of cancer waiting time targets - May effect patient choice - May limit reconstructive option, particularly in units without microvascular surgery Patient may require unexpected radiotherapy/chemotherapy
Delayed breast reconstruction	Adjuvant treatments completed well in advance of reconstruction No risk of delay to adjuvant treatment More achievable expectations No time pressure from cancer waiting time targets	Need to replace skin - Skin expansion (unpredictable if had post-mastectomy radiotherapy) - Import skin with autologous reconstruction Often 2 or more procedures Need to delay reconstruction post radiotherapy >9 months Patient has to live with simple mastectomy

1.2.4 Current Trends in Breast Reconstruction

The 2008 UK National Mastectomy and Breast Reconstruction audit (NMBRA) collected data on women undergoing mastectomy with or without reconstruction in the NHS and private sector over a nine month period as part of treatment of breast cancer. The aim was to evaluate current clinical practice and outcomes in mastectomy with or without reconstruction, the provision and access to reconstruction and the quality of information provided to women. NMBRA estimated only 21% of women were under-going immediate breast reconstruction. Implant-based reconstruction accounted for 37%, autologous with an implant 22% and autologous alone 41% (12). In 2012 Hospital Episode Statistics (HES) data indicated over 16000 immediate reconstruction procedures were performed in NHS hospitals in England, compared to 8389 in 1996. Greater than 85% were implant-based (21). In the US an increasing trend in immediate breast reconstruction between 1998 and 2008 was also identified (21% vs. 38%) with an average increase in implant based reconstructions of 11% per year. (57).

1.2.5 Outcomes in breast reconstruction

Outcome measures can be reported by the patient or professional covering clinical, short-term post-operative complications and long-term, aesthetic and functional domains.

Measuring outcomes in Breast

The optimum way to collect reliable, objective outcome data is prospectively by an independent assessor. Any outcome assessed by the treating surgeon will be subject to bias. Retrospective data collection is less accurate. To enable data to be comparable and generalizable standards have to be set, with strict definitions of outcomes prior to data being collected.

Clinical outcomes

There is currently no universal data collection tool for monitoring post-operative complications and long-term clinical outcomes after breast reconstruction. A systematic review by Potter et al. critically appraising 134 RCTs and large cohort studies on the reporting of complications after breast reconstruction revealed only 19% of the complications were defined and the definitions lacked consistency. There was disparity between the methods and results (53%) and important information to translate the results such as length of follow-up and risk factors were omitted in 35% and 43% respectively (58).

Aesthetic outcomes

There is no widely accepted, validated aesthetic scale available (59). Maass et al. (60) critically appraised the 12 identified professional aesthetic assessment scales in the literature used for assessing post-mastectomy breast reconstruction, using a modified version of the Scientific Advisory Committee's Medical Outcomes Trust criteria. They evaluated the following characteristics, which they felt the ideal scale should adhere to; development of conceptual framework, reliability, validity, responsiveness, interpretability, burden for professional and patients and correlation with patient reported outcomes, giving a score out of seven (the higher the score the more criteria were met).

The most frequently used scale was the 'Four-point' by Vrieling et al. (61) scoring 3. This graded scar, size, shape, nipple position, shape of areolar, skin colour and global cosmetic result on a scale of 0 (excellent) to 3 (poor). The highest scoring scale was the 'Ten-point' by Visser et al. (62)(Table 3) scoring 4.5. The "Ten-point" scale lacked in responsiveness and interpretability, however all scales scored zero in these two categories, with a wide range of inter and intra-rater agreements (reliability). Although the 'Four-point' scored higher in reliability it fell below in other characteristics and has never been validated for use in breast reconstruction.

Table 3 10-point scale used in the assessment of aesthetic outcomes after breast reconstruction by Visser et al. (62)

Characteristic	Scale
Breast volume	1 (very dissatisfied) 2 3 4 5 (very satisfied)
Breast shape	
Breast symmetry	
Breast scars	
Nipple/NAC	
General satisfaction	1 (extremely dissatisfied) 2 3 4 5 6 7 8 9 10 (extremely satisfied)

A systematic review of aesthetic assessment in breast reconstruction found 92% were performed by professionals alone with 55% being plastic surgeons and the remaining a combination of plastic surgeons, nurses and junior doctors (60). Commonly photographs were used (60), having the assessor(s) blinded to reconstructive procedure. Different results were found between healthcare professionals with varying expertise (63), with junior doctors giving overall higher scores (better cosmetic outcome) than consultants. When compared with patients evaluations of cosmesis, consultants gave overall lower scores (62), indicating those with more expertise are generally more critical of the outcomes, although the difference in scores were not significant.

Patient reported outcomes

The ultimate goal in breast reconstruction is patient satisfaction, however very few studies focus on this as their primary outcome. It is also important to have patient reported outcomes data to aid other women in decision making regarding their reconstruction. Patient reported outcome measures (PROMs) are usually in the form of a questionnaire in order to gain the patient's own views. To ensure useful information is gained i.e. the measure is reliable and valid, it has to undergo thorough developmental and psychometric testing followed by further validation in the population it will be used by. The most frequently used validated tool for assessing PROMs in implant-based breast reconstruction is BREAST-Q (64-72). Others include WHO QOL-BREF (73), FACT (74) and EQ-5D (75). Many studies however use their own variation of a validated tool or a self-designed non-validated questionnaire (45, 76-84) often using a Likert scale design.

BREAST-Q is a validated, procedure specific tool developed by Dr Pusic comprising of domains in satisfaction with breasts and nipples, satisfaction with outcome, psychosocial, sexual and physical well-being, satisfaction with information and staff (85). BREAST-Q was meticulously developed in three phases and its validation on over 15000 patients has proven it to be highly reliable, valid and responsive (86). Response bias is important to consider as the highly satisfied or dissatisfied can be over represented in questionnaire based feedback (87).

1.3 Capsular Contracture

1.3.1 Definition

An inflammatory response is initiated on implantation of a medical device resulting in the formation of a fibrous capsule. Capsular contracture is when this capsule around the breast implant becomes thickened, firm and tight causing pain and distortion of the implant. It remains one of the most common and unpredictable long-term complications in implant-based breast reconstruction, with reported rates as high as 25% (88). Causing physical and psychological distress for the patient, effecting cosmesis, quality of life and leading to further surgery, capsular contracture is a major problem within breast surgery.

1.3.2 Foreign body reaction

The foreign body reaction occurs at the tissue-implant interface. The response starts within minutes of the initial injury, blood and the implant interact, coagulant proteins adhere to the implant and one another forming the provisional protein matrix. The release of cytokines, chemokines, mitogens and growth factors lead on to acute inflammation. This is followed by chronic inflammation over the first two to three weeks with granulation tissue formation, ending in the formation of a fibrous capsule around the implanted device (89, 90), Figure 5. The foreign body reaction can be present for the lifetime of the device (91).

During the acute and chronic inflammatory phases the granulation tissue forms. It is composed of cells including macrophages, fibroblasts and sometimes myofibroblasts in a matrix of predominantly collagen III, supporting angiogenesis and is the precursor to the fibrous capsule formation. Fibroblasts proliferate in the granulation tissue and are active in the formation of collagen and other extracellular matrix substances e.g. fibronectin. Towards the end of this stage fibroblast to myofibroblast differentiation occurs then apoptosis of cells end the formation of granulation tissue (92, 93). In normal skin and scarring this marks a mature wound, however when there is an increase in or prolonged presence of myofibroblasts, hypertrophic and keloid scars can occur (94, 95). This finding is also present in Dupuytren's contracture, a condition where fibrous tissue forms under the palmar fascia (96). Fibroblast to myofibroblast differentiation can be influenced by a number of cytokines and proteins including TGF-β and fibronectin (97). Over the following weeks/months collagen III undergoes remodelling and is replaced by collagen I which becomes the fibrous capsule. In pathological scars, especially keloid there is a higher collagen I to III ratio (98). Dysregulation in various stages of the reaction can lead to over production of fibrous tissue.

The response can be influenced by patient related factors such as poor nutrition, diabetes and steroid use and local factors such as the degree of injury caused by the implantation, the site of implantation and its blood supply (90). Physical and chemical properties and surface topography of the implanted device can also impact the degree of the response. Smooth surfaces e.g. breast implants have a higher fibrous content, whereas rough surfaces e.g. vascular grafts have a higher macrophage and foreign body cell content (90).

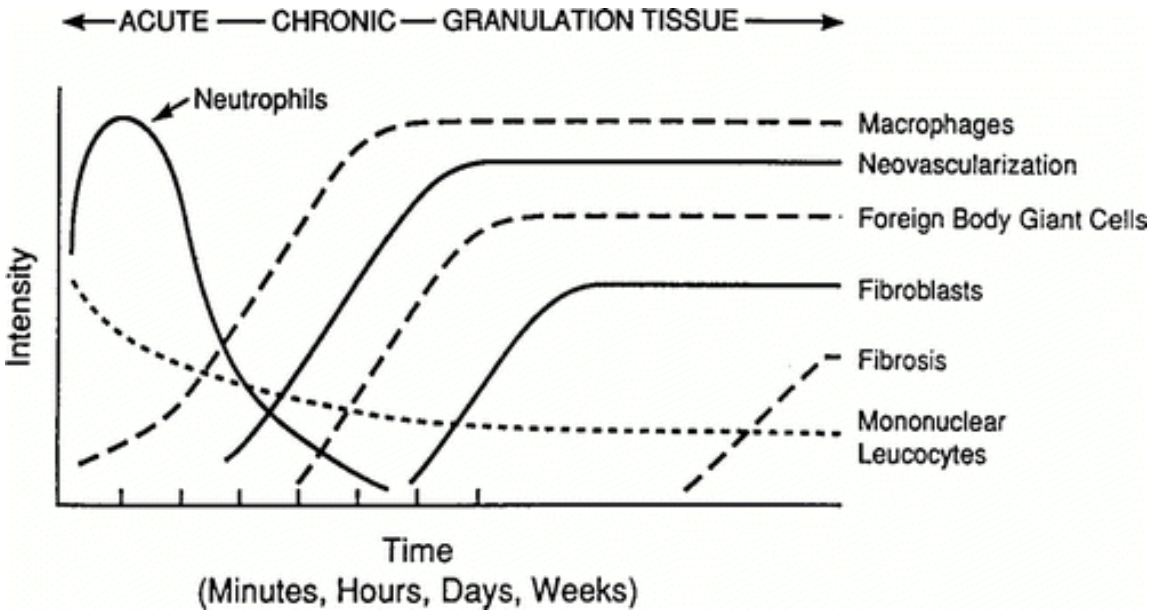


Figure 5 The temporal variation in the acute inflammatory response, chronic inflammatory response, granulation tissue development and foreign body reaction to implanted biomaterials. The intensity and time variables are dependent upon the extent of injury created in the implantation and the size, shape, topography and chemical and physical properties of the biomaterial. Reproduced with permission from Anderson (2001); Biological Response to Materials; Annual review of materials research (90)

1.3.3 Normal and contracted capsule histoarchitecture

The fibrous capsule is formed around the implant as the final stage of the foreign body response in an attempt to segregate the implant from the surrounding tissues. The capsule is composed of three layers, Figure 6;

1. Inner layer (directly adjacent to the implant) described as a thin synovial-like metaplasia, containing macrophages, fibroblasts and occasional multinucleated giant cells as well as adhesive proteins such as fibronectin (99-101). The presence of this layer is observed more with textured implants and is found to decrease with increase in implant duration (102, 103)
2. Middle layer which is highly cellular composed predominantly of immune cells within loosely arranged connective tissue including an internal vascular supply. Collagen fibres are orientated parallel to the implant (100, 104)
3. Outer layer of dense connective tissue, rich in collagen fibres aligned perpendicular to the implant (100, 104, 105) and also containing myofibroblasts (99, 106)

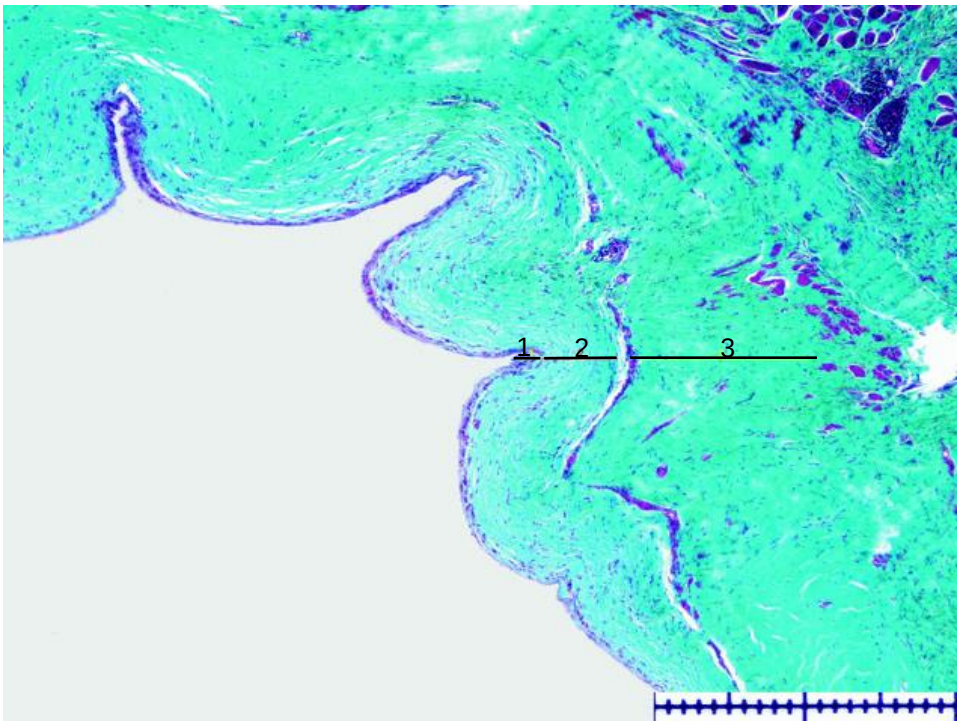


Figure 6 Three-layer composition (Masson Goldner stain; magnification, 4x): 1, inner layer, with a hyaline membrane toward the implant (synovia-like metaplasia); 2, middle layer, with loosely packed network of collagen fibres including internal vascular supply and showing increased cellularity; and 3, outer layer, with dense connective tissue. Reproduced with permission from Prantl et al. (2007); Clinical and morphological conditions in capsular contracture formed around silicone breast implants. Plast. Reconst. Surg (100)

Contracted capsules are described as being more cellular with increased numbers of fibroblasts and myofibroblasts (101, 107). Although myofibroblasts play a significant role in tissue repair, persistent activation of myofibroblasts can lead to a pathological response contributing to fibrosis (108). Collagen fibres are thick and highly aligned in contracted capsules whereas they are thin, loosely arranged and multi-directional in non-contracted capsules, figure 7 (101). Contracted capsules appear to have a more vascular outer layer which non-contracted capsules do not (101). Capsule thickness can vary significantly however is positively correlated with implantation time. Non-contracted capsules are significantly thinner than contracted (101, 103, 107) but the thickness has not been shown to correlate with degree of contracture (i.e. Baker II, III or IV) (100). There was a significant increase in capsule thickness when calcification and silicone was present within the capsule however the trend of higher baker grade with these findings did not reach statistical significance (103).

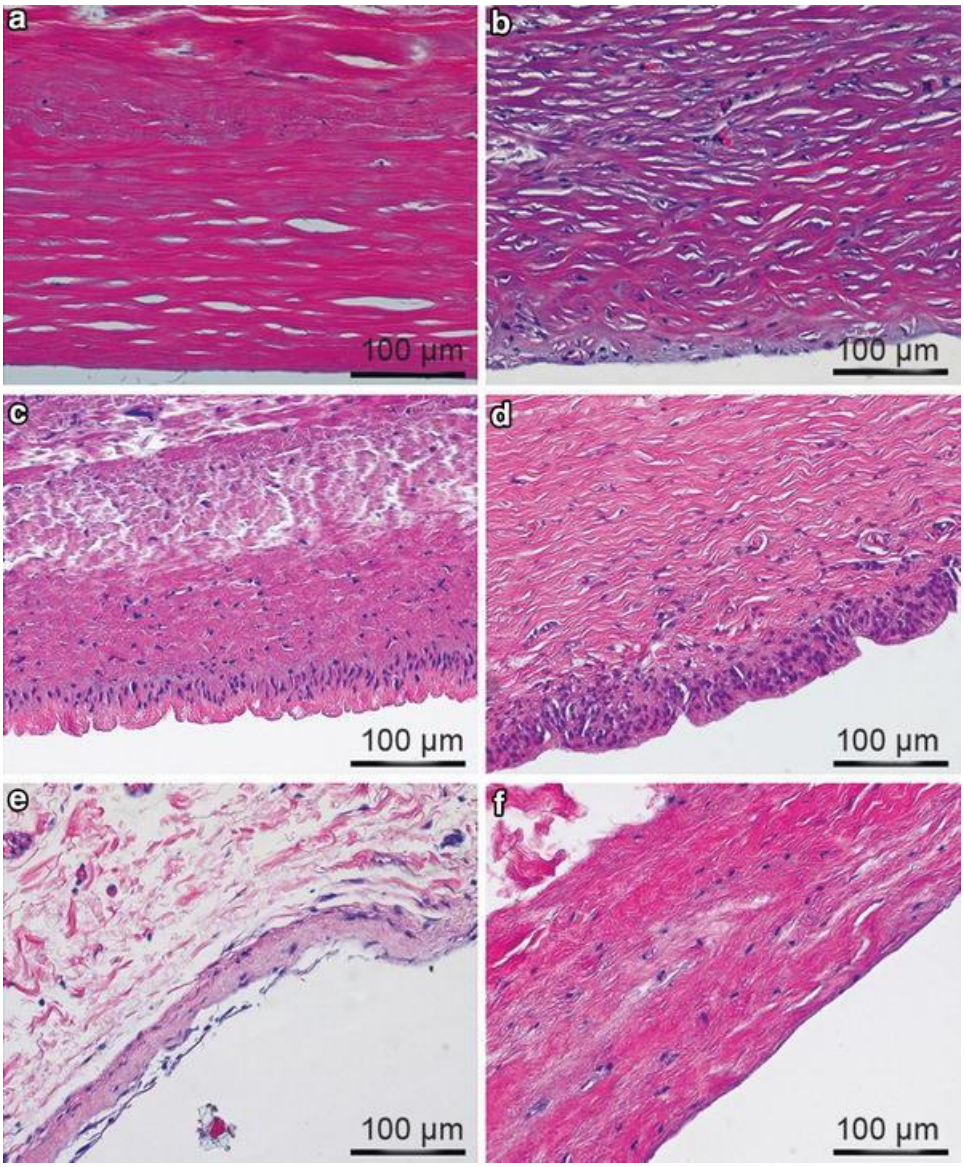


Figure 7 Hematoxylin and eosin staining of human capsules (magnification ×20, *scale bar* 100 µm). All images are oriented with the implant-tissue interface in the *lower portion* of the image. **a** Baker IV contracted capsule with low cellularity and thick dense bands of highly aligned fibers taken from a smooth silicone implant after 3 years of submuscular implantation. **b** Baker IV contracted capsule with increased cellularity and thick dense bands of highly aligned fibers taken from a smooth silicone implant after 3 years of submuscular implantation. **c** Baker II capsule with morphology consistent with synovial metaplasia taken from a textured saline implant after 10 years of dual plane implantation. **d** Baker III capsule with morphology consistent with synovial metaplasia taken from a smooth silicone implant after 15 years of submuscular implantation. **e** Thin Baker I capsule with loosely arranged fibers taken from a smooth saline implant after 3 years of submuscular implantation. **f** Baker I capsule with low cellularity and loosely arranged fibers taken from a smooth saline implant after 12 years of subglandular implantation. Reproduced with permission from Bui et al. (2015); Histological characterization of human breast implant capsules. Aesthetic Plast Surg (101)

1.3.4 Pathogenesis

The reason why capsules become contracted is unknown. Believed to be multifactorial, two proposed mechanisms are; excessive immunological foreign body response (99, 103, 109-111) and low-grade, subclinical infections and biofilms (112-116).

Excessive foreign body/inflammatory response

In the absence of other contributing factors such as haematoma or infection the excessive response is likely to be secondary to the foreign body (implant) alone. Dysregulation of any stage of the foreign body reaction can lead to fibrosis. The very initial interaction between the blood and implant where protein adsorption and cell attachment occurs leading to cytokine and chemokine release may have a significant impact on the extent of the foreign body reaction (117-119). It is thought that the surface topography of implants on a micro and nano metric scale can influence this stage in the response (120-122). Barr et al. demonstrated a difference in binding affinity of pro-inflammatory and anti-inflammatory proteins to commercially available implant surfaces while Cappellano et al. demonstrated these surfaces can induce secretion of proinflammatory cytokines (121, 122). Down regulation of pro-inflammatory/pro-fibrotic genes and reduced secretion of pro-inflammatory/pro-fibrotic cytokines has also been demonstrated in different biomimetic silicone topographies (120).

Macrophages, one of the predominant cells in mounting a host response to any insult to the body, are abundant in the chronic inflammatory phase of the foreign body reaction and produce the cytokine transforming growth factor-β1 which regulates fibroblast to myofibroblast differentiation. Normal collagen and extracellular matrix deposition is dependent on healthy fibroblasts. Silicone can damage macrophages leading to the over production of TGF-ß and IL1, a pro-inflammatory cytokine (123). Both TGF-ß and IL1 can then increase fibroblast proliferation and fibroblast to myofibroblast transition, increasing collagen production and therefore fibrosis (124). When myofibroblasts persist beyond the granulation phase of the foreign body response it is thought excessive extra cellular matrix deposition and pathological contracture occurs (89). Contracted capsules are found to contain increased numbers of myofibroblasts (101, 107).

Further dysregulation of components involved in the inflammatory response have been demonstrated in contracted breast capsules supporting this theory (Table 4), for example increased expression of tumour necrosis factor–α, a pro-inflammatory cytokine (125) and reduced expression of TSG-6, a pluripotent protein with anti-inflammatory properties (111).

Table 4 Summary of Cells, Genes and proteins associated with contracted breast capsules, adapted with permission from Kyle (2015); Identification of biomarkers for capsular contracture formation and novel biomimetic breast implant surface design and development. Thesis, University of Manchester (126)

Cell/Gene/Protein	Expression/effect in higher Baker grades	Author	Year
Interleukin 2	Increased	Wells et al (127)	1994
Hyaluronic Acid	Increased	Wells et al (127)	1994
MMP:TIMP ratio	Decreased ratio	Ulrich et al (128, 129)	2004, 2009
Aminoterminal propeptide of procollagen type 3	Increased	Ulrich et al (128)	2004
T-lymphocytes	Silicone induced dysregulation	Wolfram et al (99)	2004
TNF-α	Increased	Tan et al (130)	2010
Cysteinyl leukotriene receptor-2	Increased	Tan et al (130)	2010
Collagen type 3	Decreased	Tan et al (130)	2010
Tumour suppressor gene 6	Decreased	Tan et al (111)	2011
T regulatory and TH17 cells	Increased production of cytokines (IL17, IL8, IL6, TGFß1 & interferon gamma	Wolfram et al (131)	2012
IL8	Increased	Kyle et al (132)	2013
TIMP4	Decreased	Kyle et al (132)	2013
Mast cells	Activation of fibroblasts through increased secretion of histamine, renin-ANG II & TGFß	Brazin et al (133)	2014
Fibroblasts	Increased pro-inflammatory & pro-fibrotic genotype & phenotype	Kyle et al (134)	2015
Lysyl oxidase	Increased	Poh et al (135)	2018
Toll-like receptors 2 and 6	Increased	Bachour et al (136)	2019

Infection

Infection as a cause of capsular contracture was first proposed by Burkhardt et al. in 1981 (137). However, many cases of capsular contracture were found to form without gross evidence of infection, this led to the recognition of bacterial biofilms as a contributory factor (138). A biofilm - "a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface" (139) drives a chronic inflammatory response. During the inflammatory process fibroblasts grow leading to further collagen deposition, differentiate in to myofibroblasts and subsequent contracture occurs. Using an in-vivo model (inoculating the peri-prosthetic pocket in pigs with staphylococcus epidermidis over a 13 week period) Tamboto et al. demonstrated biofilm is associated with a four-fold increase risk of developing capsular contracture (116). Further studies inoculating the peri-prosthetic pockets in animal models found an increase in capsular contracture (113, 114). Not all implants/capsules which become contracted are found to have a biofilm (112). Anderson suggested a prolonged acute inflammatory phase of the foreign body response indicated the presence of infection (90). Infection and biofilms are therefore further factors that can dysregulate the foreign body response resulting in capsular contracture rather than a true cause.

1.3.5 Risk factors for capsular contracture

Factors which have been associated with an increased risk of capsular contracture are tissue trauma, haematoma, infection; radiotherapy and implant surface and rupture (44, 78, 140-150), events which could drive or dysregulate the inflammatory response.

Haematoma

Haematoma caused a two-fold increase in rate of capsular contracture in a study of 3495 implants with a mean follow-up of three years (146). Of 62 patients with haematomas, 12 developed capsular contracture compared to 412 of 3432 without. In a study of 1655 implants, haematoma was associated with a significant increase in capsular contracture (29% vs. 13%) with a more rapid occurrence of the contracture (147).

Radiotherapy

In a prospectively collected database of 2133 implant based reconstructions (15% received radiotherapy); with annual assessment by the operating surgeon and a mean follow-up of 58.8 months, there was a significant increase in capsular contracture (44). Grade III capsular contracture in the radiotherapy group was 39.7% vs. 5.9% in the non-radiotherapy group and grade IV 6.9% vs. 0.5% respectively. A systematic review of pre and post reconstruction radiotherapy demonstrated a pooled severe capsular contracture rate of 25% (95% CI 10-45) in 68 breasts that had radiotherapy pre-reconstruction and 32% (95% CI 20-46) in 818 breasts that had radiotherapy post-reconstruction. Both prospective and retrospective studies were included and mean follow-up ranged from 15 – 96 months; however, this is higher than the rates demonstrated from the core studies (Table 5).

Studies have suggested radiotherapy can increase the number of myofibroblasts by TGF-ß upregulation and endothelial-mesenchymal transition (EndoMT) (151-153) which are then responsible for excessive collagen and extra cellular matrix production and increased fibrosis (89).

Implant rupture

Silicone particles have been found in contracted capsules (103, 107), in a study of 26 contracted capsules high silicone levels were present in eight (31%). A greater capsule thickness was associated with a stronger presence of silicone ($p<0.001$), however a significant correlation between Baker grade and presence of silicone has not been made. Implant rupture can present with symptoms consistent with capsular contracture, change in breast size, shape, texture and pain however rupture rate was no different between symptomatic (72%) and asymptomatic (71%) women having implants removed in a retrospective studies evaluating 592 removed implants (154).

Silicone can damage macrophages, one of the key cells in the chronic inflammation phase of the foreign body reaction, in turn leading to the over production of TGF-ß and IL1, a pro-inflammatory cytokine (123) both of which increase fibroblast proliferation increasing collagen production and therefore fibrosis (89).

Implant surface

Surface topography can play a significant role in the intensity of the foreign body response from the initial cell interactions to how the collagen is organised during the capsule formation. This is discussed in more detail in the preventative measures section.

1.3.6 Incidence

The most comprehensive data we have reporting incidence of capsular contracture over time comes from the 'Core Studies'. In 1992, in response to concerns about the lack of safety information, the Food and Drug Administration (FDA) removed and banned the use of silicone implants. However, due to public health demand the FDA supported their continued use in reconstruction and correction of congenital deformities with the condition that manufacturers performed studies assessing long-term safety and effectiveness. These "Core Studies" required the manufacturers to perform clinical assessments annually for 10 years, reporting outcomes to the FDA who then released interim reports to the public. One of the key findings of these studies was that capsular contracture can occur at any time point post implantation but incidence increases with time (46, 103, 155-163)(Table 5). In primary augmentation, capsular contracture rates were 1.9% at three years and 19.1% at ten years with Allergan Natrelle® silicone gel-filled implants (157, 163).

Table 5 Core Studies (46, 155-163): cumulative incidence rates over time of Grade III/IV capsular contracture in primary reconstruction and 95% confidence intervals calculated using Kaplan-Meier analysis

	3 years % (95% CI)	5 years % (95% CI)	6 years % (95% CI)	8 years % (95% CI)	9 years % (95% CI)	10 years % (95% CI)
Allergan Natrelle® silicone gel-filled implants	5.9 (3.4-10.2)		10.7 (7.1-16.0)			24.6 (16.2-36.2)
Mentor Memory Gel® silicone gel-filled implants	8.3 (4.7-11.9)		13.7 (9.7-19.1)	15.3 (11.1-20.9)		
Sientra® Silimed gel-filled implants		10.6 (7.0-16.0)		12.8 (8.6-18.8)	14.4 (9.8-20.8)	

1.3.7 Assessment of capsular contracture

Subjective assessment of capsular contracture

Baker Classification

Baker grade was introduced in 1975 as a classification system of capsular contracture in breast augmentation (164). A modified scale has since been described for use in implant based breast reconstruction (Table 6) (165). This subjective scoring system is widely accepted and commonly used in the clinical setting; however, it has not been formally validated in breast augmentation or reconstruction.

Table 6 Baker classification (164, 165)

Original Baker classification of capsular contracture after breast augmentation		Classification of capsular contracture after implant-based breast reconstruction	
Class I	Breast absolutely natural; no one could tell breast was augmented	**Class IA**	Absolutely natural, cannot tell breast was reconstructed
		Class IB	Soft, but the implant is detectable by physical examination or inspection because of mastectomy
Class II	Minimal contracture; I can tell surgery was performed, but the patient has no complaint	**Class II**	Mildly firm reconstructed breast with an implant that may be visible and detectable by physical examination
Class III	Moderate contracture; patient feels some firmness	**Class III**	Moderately firm reconstructed breast, implant is readily detectable but the result may still be acceptable
Class IV	Severe contracture; obvious just from observation	**Class IV**	Severe capsular contracture with an unacceptable aesthetic outcome and/or significant symptoms requiring surgical intervention

Objective assessment of capsular contracture

Tonometry

Applanation tononmetry is an objective measurement of intramammary pressure to evaluate breast hardness in capsular contracture (166, 167). A flat transparent disc (Figure 8) is placed on the breast and the area of contact is quantified in relation to the pressure applied to determine a score between zero (hard) and ten (soft). Baseline tonometry readings in non-operated breasts range from four to ten (168). One study of 120 augmentations found good correlation between Baker grade and mean tonometry readings. The contact area however may be influenced by the size of the breasts therefore serial measurements may be more accurate to account for differences between patients and tissues. In animal models tonometry was able to detect tissue softening following lipoinjection of capsules, despite no significant histological change in the explanted capsules (169). Although tonometry identifies capsule formation (170), it may be no more sensitive than clinical assessment (171).

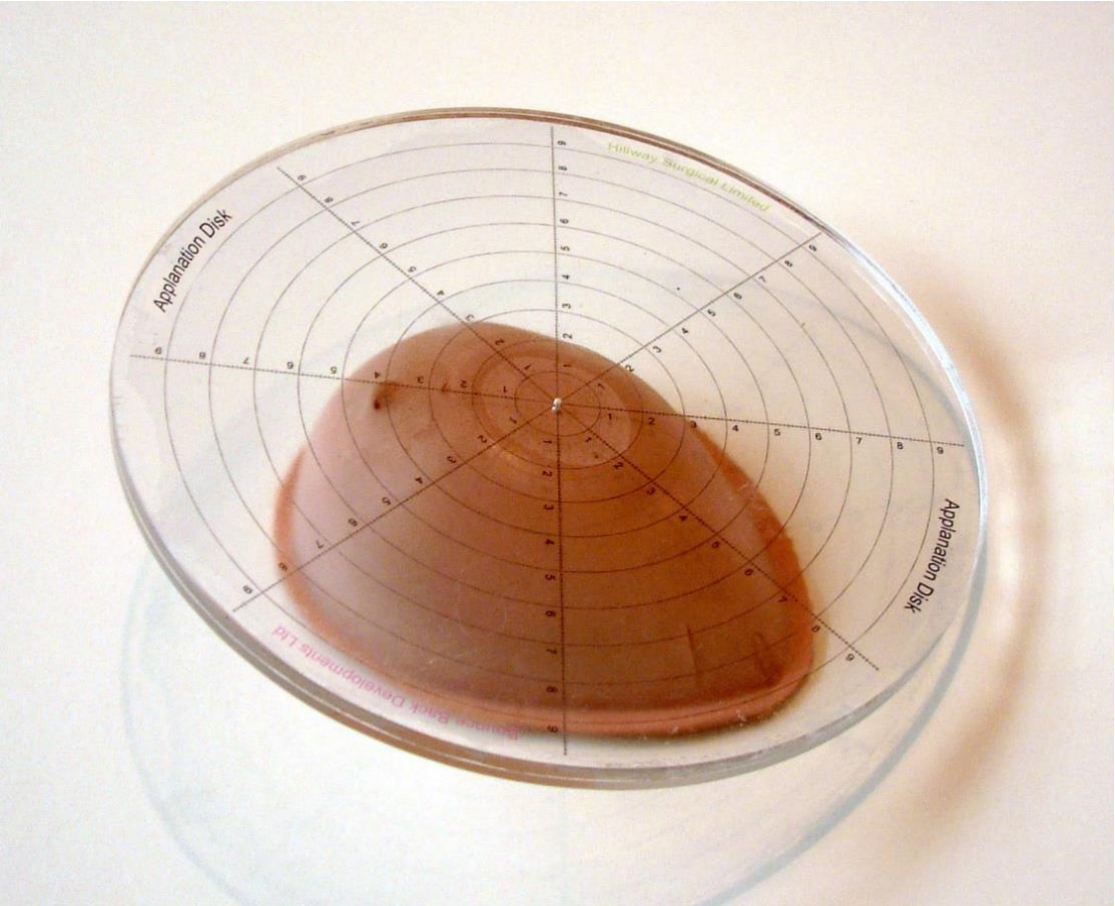


Figure 8 Applanation tonometer used to measure intramammary pressure

Mammary Compliance

Mammary compliance or breast compressibility is calculated by the difference in the diameter of the breast at rest and when compression is applied by a known force using callipers. Mammary compliance values correlate with Baker grade (168, 172, 173). Using untreated breasts as a control (n=59), compliance values matched those of the augmented/reconstructed breasts classified as baker grade I (n=45) (172). In a study of 120 augmented breasts mean mammary compliance values increased as Baker grade increased (173). All studies concluded that readings were independent of the thickness of overlying soft tissue reflecting accurate assessment of the capsule (168, 172, 173).

Elastography

Ultrasound elastography, a technique for quantitative assessment of tissue stiffness, had been developed and used in the diagnosis of breast lesions over the past 20 years but was first described for the assessment of capsular contracture in a case report in 2011 (174). A study of only 11 patients, demonstrated high correlation between the Baker grade and elastography measurement, in 77% of cases the elasticity grade matched the Baker grade (175).

1.3.8 Management of capsular contracture

Preventative measures

Addressing potential causative mechanisms and risk factors, techniques have been proposed to reduce incidence of capsular contracture. These include; bloodless dissection, pocket irrigation, minimising contact with the implant, avoiding peri-areolar incisions and using textured implants (88, 140, 144, 176-179). Other techniques to reduce contamination of the implant such as glove changes and introduction sleeves have not been studied specifically in their effect on capsular contracture formation.

Pocket Irrigation

Both in-vitro and clinical studies to determine the best mixture for irrigating and the clinical outcomes of its use have been performed (176, 180, 181). In a 6 year prospective study, a threefold reduction in capsular contracture in breast reconstruction was demonstrated when a solution of 50,000 units of bacitracin, 1g of cefazolin, 80mg of gentamicin and 500ml of normal saline was used compared to saline alone. Although two independent examinations were performed, mean follow-up was only 14 months. In a retrospective review of 1244 augmentation patients capsular contracture rate was 2.2% with 50% betadine pocket irrigation, this further reduced to 0.5% when the nipple areolar complex was covered with a betadine soaked swab (n=211), however mean follow-up was only 5 months in this group (177)

Incision placement

In breast augmentation, there is a greater than 15-fold increase in capsular contracture when a peri-areolar incision is used compared to an inframammary incision (9.5% and 0.59%) (182). This may reflect the colonisation of the ductal system with bacteria resulting in a five times higher bacterial count found peri-areolar compared to inframammary (183). However, the applicability of this to nipple sparing (or nipple sacrificing) breast reconstruction, where the duct system is divided (and removed) irrespective of incision placement, is less clear.

Textured implants

A meta-analysis of 16 RCTs and two retrospective studies (n=8,458) comparing implant shell type in both augmentation and reconstruction concluded smooth breast implants were more likely to be associated with capsular contracture (RR 3.10, 95% CI, 2.23-4.33) (184). Textured implants appear to disrupt the organised arrangement of fibroblasts and myofibroblasts which occur around smooth implants, this disruption is advantageous in reducing the formation of capsular contracture (185-187). In one study contracted and non-contracted capsules from textured implants were found to be negative for myofibroblasts (n=8), whereas 35% of smooth capsules (n=40) stained positive for myofibroblasts ($p<0.05$) (101). Significantly higher fibroblast adhesion is seen in textured implants suggesting they promote tissue ingrowth and therefore produce an enhanced, stable host-prosthesis interface promoting decreased capsular contracture (188). In-vitro, textured implants had 72-fold more bacteria at 24hrs compared to smooth implants. However, in-vivo this did not translate to a difference in biofilm or presence of capsular contracture at 20 weeks in a study of 121 implants in pigs (189).

Polyurethane implants are silicone implants coated in polyurethane foam, giving a furry appearance and feel. A systematic review concluded reported rates of capsular contracture with polyurethane implants are 3-30 times lower than textured silicone (88). However, it was felt that the true incidence is likely to be higher as the data available was from a single centre and retrospective studies lacking in a description of how patients were assessed for capsular contracture. Despite positive clinical findings, in animal models polyurethane coated implants have been associated with a more intense foreign body reaction and myofibroblasts presence (190, 191). It is difficult to ascertain in the animal model whether these features would translate into higher rates of capsular contracture in the long term.

Surgical management of capsular contracture

Often surgical intervention is required to improve the cosmetic appearance and relieve symptoms especially in grade III and IV capsular contracture (Table 6). Data from the Core Studies (155-163) demonstrated 15% of revisions and 18% of implant removals were secondary to capsular contracture. Capsulotomy release of the capsule or capsulectomy excision of the capsule can be performed however capsular contracture can still recur. Rates of capsular contracture after revision reconstruction can be as high as 23% (155-163). Cheng et al. (192) described wrapping implants in ADM after capsulectomy in 16 breasts with no recurrence of capsular contracture over an average of 9 months follow-up. Patients may require further reconstruction with autologous tissue or prefer to have their reconstruction removed completely, despite the poor cosmetic result.

Non-surgical management of capsular contracture

Non-surgical methods including massage and ultrasound have been suggested but there is little evidence of their continued success. On average six sessions of ultrasound therapy in 52 women (with grade II-IV contractures) resulted in an improvement of at least one Baker grade in 82% at 1 year follow-up. However, there was no further follow-up to assess whether these improvements were sustained (193). Pirfenidone, an oral anti-fibrotic drug, given prophylactically reduced collagen content by 50% along with inflammation and capsule thickness in a study of 10 rats (194). It has not been studied in the human population. Zafirlukast, an oral leukotriene receptor antagonist, has the most successful results (195-199) but remains unlicensed for this use. Prophylactic zafirlukast reduced the fibroblast and collagen layer and overall capsule thickness around discs of tissue expander material which were implanted into 40 rats (199). Mammary compliance improved in a study of 120 women, diagnosed with capsular contracture and treated with a 6 month course of zafirlukast, compared to controls, however, the effect regressed after cessation of therapy (198, 200).

1.4 Acellular dermal matrices

1.4.1 What are acellular dermal matrices?

Acellular dermal matrices (ADMs) are decellularised human or animal derived tissues such as dermis. The collagen and extracellular matrix is used as a scaffold for the host tissues to grow into (201).

1.4.2 What are acellular dermal matrices used for?

ADMs were first introduced in 1993 as a replacement tissue in burns injuries (202) but are now used in the management of herniae, chronic wounds and for many reconstructive procedures. Breuing et al. first described their use in breast reconstruction to support, cover and disguise the lower part of the breast implant (Figure 3, page 27)(31). They are now also used in delayed reconstruction, revision surgery for reconstruction and augmentation and primary augmentation (203, 204).

1.4.3 Available acellular dermal matrices

A porcine dermis derived ADM (Strattice™) was the first to be introduced to the UK in 2008 for use in immediate breast reconstruction. There are now several variations available derived from different animal tissues and often undisclosed processing techniques (Table 7). Human derived acellular dermal matrices (HADM), widely used in the USA, are not licensed for use in the UK. Data comparing clinical outcomes between the products is limited. Exploratory analysis from the iBRA study, a non-randomised multi-centre prospective cohort study (n=2655 immediate implant based reconstructions), showed no association between type of mesh and short-term outcomes (205).

1.4.4 Advantages of ADM-assisted immediate implant based breast reconstruction

Benefits described with ADM use are highly subjective but are i) improved aesthetic results (63, 206) from improved lower pole projection, giving a more natural ptotic looking breast (31, 63, 207-209) ii) improved inframammary fold definition (206, 209-211); iii) reduced pain (207, 212) and iv) shorter operating and recovery times (31), v) increased intra-operative fill volume and decreased number of expansions after two-stage procedures (211), vi) improved implant coverage, vii) less rippling and less implant displacement (206, 213). There is very little literature on the long-term outcomes, especially in the UK population. Limited evidence suggests that ADMs reduce the rate of capsular contracture (63, 206-208).

1.4.5 Challenges in ADM-assisted immediate implant based breast reconstruction

Adequate skin flap perfusion and vascularity after skin sparring mastectomy is important to reduce mastectomy flap necrosis and potentially subsequent implant loss. Reported rates of flap necrosis are as high as 25% and account for up to 40% of implant-based reconstruction failures (214). In order for ADMs to integrate and remodel with the mastectomy skin flaps an adequate blood supply is needed (215). Idiopathic erythema can occur termed “red breast syndrome”, which can be mistaken for infection, leading to unnecessary treatment. The aetiology is unknown but foreign body reaction, hypersensitivity reaction, reaction to chemicals and processing techniques have been suggested (216-218). In-vitro, chemically cross-linked ADMs induce inflammatory cells (219, 220).

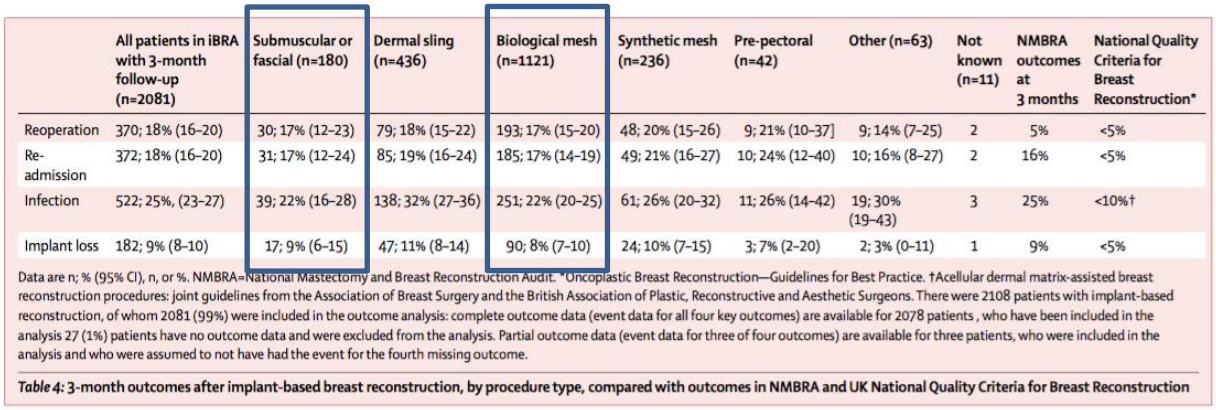
Table 7 ADMs available in the UK for use in breast surgery

Product (Provider)	Derivation	Chemically Cross-linked	Chemical preservatives	Mode of sterilization
Strattice™ (LifeCell)	Porcine dermis	No	Yes Polysorbate 20	E-beam irradiation
Artia™ (Life Cell)	Porcine dermis	No		
Braxon® & Native® (QuaMedical)	Porcine dermis	No	No	
Cellis® (Meccellis Biotech)	Porcine dermis		No	
MesoBioMatrix® (DSM)	Porcine peritoneum	No	No	Ethylene oxide
Biodesign® (Cook)	Porcine small intestinal submucosa	No		Ethylene oxide
SurgiMend® (Integra)	Bovine dermis	No	No	Ethylene oxide
Veritas® (Synovis)	Bovine pericardium	No	Yes Sodium hydroxide	Irradiated

1.4.6 Clinical outcomes in immediate ADM-assisted implant based breast reconstruction

Short-term outcomes

Initial complication rates as high as 48.5% (221) with the use of ADM in breast reconstruction, in single centre case series, suggested a learning curve effect. Complication rates in the first year (21.4%) were double that of subsequent years (10.9%) in a retrospective review of 331 consecutive single stage ADM-assisted implant based reconstructions (222). Larger published series are limited by lack of control groups. The iBRA Study, a prospective, non-randomised, multicentre cohort study of 2108 consecutive patients who underwent 2655 immediate implant based reconstructions found no difference in short term outcomes between submuscular and biological mesh assisted reconstructions in terms of re-operation, re-admission, infection and implant loss, figure 9 (205).



	All patients in iBRA with 3-month follow-up (n=2081)	Submuscular or fascial (n=180)	Dermal sling (n=436)	Biological mesh (n=1121)	Synthetic mesh (n=236)	Pre-pectoral (n=42)	Other (n=63)	Not known (n=11)	NMBRA outcomes at 3 months	National Quality Criteria for Breast Reconstruction*
Reoperation	370; 18% (16–20)	30; 17% (12–23)	79; 18% (15–22)	193; 17% (15–20)	48; 20% (15–26)	9; 21% (10–37]	9; 14% (7–25)	2	5%	<5%
Re-admission	372; 18% (16–20)	31; 17% (12–24)	85; 19% (16–24)	185; 17% (14–19)	49; 21% (16–27)	10; 24% (12–40)	10; 16% (8–27)	2	16%	<5%
Infection	522; 25%, (23–27)	39; 22% (16–28)	138; 32% (27–36)	251; 22% (20–25)	61; 26% (20–32)	11; 26% (14–42)	19; 30% (19–43)	3	25%	<10%†
Implant loss	182; 9% (8–10)	17; 9% (6–15)	47; 11% (8–14)	90; 8% (7–10)	24; 10% (7–15)	3; 7% (2–20)	2; 3% (0–11)	1	9%	<5%

Data are n; % (95% CI), n, or %. NMBRA=National Mastectomy and Breast Reconstruction Audit. *Oncoplastic Breast Reconstruction—Guidelines for Best Practice. †Acellular dermal matrix-assisted breast reconstruction procedures: joint guidelines from the Association of Breast Surgery and the British Association of Plastic, Reconstructive and Aesthetic Surgeons. There were 2108 patients with implant-based reconstruction, of whom 2081 (99%) were included in the outcome analysis: complete outcome data (event data for all four key outcomes) are available for 2078 patients , who have been included in the analysis 27 (1%) patients have no outcome data and were excluded from the analysis. Partial outcome data (event data for three of four outcomes) are available for three patients, who were included in the analysis and who were assumed to not have had the event for the fourth missing outcome.

Table 4: 3-month outcomes after implant-based breast reconstruction, by procedure type, compared with outcomes in NMBRA and UK National Quality Criteria for Breast Reconstruction

Figure 9 Results from the iBRA study, demonstrating no difference in outcomes between submuscular and ADM reconstructions (205)

To date one American RCT comparing ADM-assisted implant/expander reconstruction and submuscular reconstruction has been published (67). However, this had to be prematurely closed due to poor recruitment. The primary outcome was postoperative pain. A total sample size of 98 was required to power the study to 90 per cent, in order to detect a two-point reduction in pain score in the ADM-assisted group. A total of 70 were recruited, 36 to the ADM-assisted group and 34 to the traditional submuscular technique group. No difference was found in levels of postoperative pain. Adverse events were similar between both groups (Table 8). The published interim analysis of safety, a secondary outcome, in a European open-label RCT comparing immediate single stage Strattice™-assisted (n=59, 91 breasts) and two-stage submuscular reconstruction (n=62, 92 breasts) showed a significant difference in outcomes between the two groups (Table 8)(223). High complications rates may be attributable to poor patient selection, lack of surgical quality assurance or the 'learning curve effect'.

Table 8 Adverse events in RCTs by McCarthy et al. (67) & Dikmans et al. (223) comparing ADM-assisted and submuscular reconstruction

	ADM-assisted		Traditional submuscular	
	McCarthy n=36	Dikmans n=91	McCarthy n=34	Dikmans n=92
Total complications	17%	46%**	15%	18%**
Infection	8%	8%	3%	2%
Haematoma	3%	3%	3%	2%
Seroma	3%	0%	9%	2%
Skin necrosis	Not reported	12%*	Not reported	1%*
Unplanned explantation	3%	26%**	0%	4%**

*p<0.05, **p<0.001

Six meta-analyses have been performed using the observational studies available (224-229) (Tables 9 and 10). No significant increased risk of unplanned return to theatre in ADM use was found when combining data from 4 papers, relative risk 1.09 (95% CI 0.63-1.90) (229). A definition of unplanned return to theatre was only given in one paper where it was for short term complications and excluded revision procedures.

Long-term outcomes

Implant malposition were found to be reduced with ADM use, using data from 2 papers, relative risk 0.21 (95% CI 0.07-0.59) (229). The follow-up period was not documented in one study and was a mean of 29 months in the other. This highlights the lack of comparative long-term follow-up data available in the literature. The studies included in the meta-analyses predominantly report on HADM use, which is common American practice. There is a paucity of data on the outcomes of xenographic ADMs, the current UK practice. The retrospective nature, lack of definitions of outcomes, assessment by the operating surgeon or a non-blinded assessor reduces the quality and comparability of the data.

Revision rates in direct to implant subpectoral HADM assisted reconstruction were comparable to those in two stage submuscular tissue expander reconstruction (20.86% vs. 20.28%) in a retrospective cohort study of 682 consecutive reconstructions, with a mean follow-up time of 5 years (range 2.5-8)(230)

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Table 9 Pooled complication rates from meta-analyses of immediate ACM-assisted breast reconstruction (2 stage tissue expander (TE) or direct to implant (DTI)) ± a traditional submuscular technique

	Newman et al. 2011 (224)		**Kim et al. 2012 (225)**		**Hoppe et al. 2011 (226)**		**Ho et al. 2012 (227)**		**Zhao et al. 2015 (228)**		**Lee et al. 2016 (229)**	
Inclusion criteria	HADM 2 stage TE or DTI reconstruction Up to July 2009		HADM 2 stage TE or DTI reconstruction or traditional submuscular technique Jan 2000-Feb 2011		HADM (AlloDerm) 2 stage TE or DTI reconstruction with a traditional submuscular technique control group Up to Feb 2011		ACM 2 stage TE or DTI reconstruction with or without a traditional submuscular technique control group 1966-Sept 2010		ACM 2 stage TE or DTI reconstruction with a traditional submuscular technique control group Jan 2010 – Feb 2015		ACM 2 stage TE or DTI breast reconstruction with traditional submuscular technique control group Feb 2011 – Dec 2014	
Exclusion criteria	Studies using xenografts Studies using graft for cosmetic surgery		Studies reporting less than 25 cases		No comparison group		Studies reporting less than 10 cases		None recorded		Single arm studies Animal studies Studies reporting less than 10 cases	
No of included papers	12 studies		13 studies reporting HADM 29 studies reporting submuscular 6 studies reporting both		7 studies		11 studies reporting ACM 5 studies reporting both ACM and submuscular		11 studies		23 studies	
	ACM	No ACM	ACM	No ACM	ACM	No ACM	ACM	No ACM	ACM	No ACM	ACM	No ACM
No. of breasts	789	N/A	2037	12847	N/A	N/A	N/A	N/A	1684	1149	N/A	N/A

Total complications %	12	N/A	15.4	14.0	N/A	N/A	N/A	N/A	22.9	20.5	22.7	20.3
Seroma %	3.3	N/A	4.8	3.5	9.4	2.0	6.9	N/A	5.0	3.3	7.7	4.5
Infection %	5.6	N/A	5.3	4.7	12.2	2.1	5.7	N/A	9.2	8.0	9.8	7.1
Flap necrosis %	3.3	N/A	6.9	4.9	N/A	N/A	10.9	N/A	N/A	N/A	10.5	6.9
Haematoma %	N/A	N/A	1.0	1.5	1.4	0.8	1.3	N/A	N/A	N/A	N/A	N/A
Reconstructive failure %	N/A	N/A	3.8	3.8	6.0	2.2	5.1	N/A	7.2	8.4	6.5	6.2
Capsular contracture %	N/A	N/A	N/A	N/A	N/A	N/A	0.58	N/A	N/A	N/A	4.9	21.2

N/A=not reported

Table 10 Relative risks for complications in ACM-assisted versus submuscular breast reconstruction

Complications	Hoppe et al. 2011 (226)		Kim et al. 2012 (225)		Ho et al. 2012 (227)		Zhao et al. 2015 (228)		Lee et al. 2016 (229)	
	No. of studies	OR (95% CI)	No. of studies	RR (95% CI)	No. of studies	OR (95% CI)	No. of studies	OR (95% CI)	No. of studies	RR (95% CI)
Total complications	N/A	N/A	6	2.05(1.55-2.70)	N/A	N/A	8	1.33(1.03-1.70)	12	1.08(0.87-1.34)
Infection	7	2.33(1.55-3.49)	6	2.47(1.71-3.57)	4	3.52(2.00-6.19)	9	1.47(1.04-2.06)	17	1.42(1.02-1.99)
Seroma	6	3.00(1.96-4.61)	6	2.73(1.67-4.46)	4	3.89(2.44-6.21)	8	1.66(1.13-2.44)	17	1.41(1.12-1.78)
Flap necrosis	N/A	N/A	4	1.56(0.85-2.85)	2	3.15(1.79-5.55)	N/A	N/A	14	1.44(1.11-1.87)
Implant loss	7	2.41(1.59-3.64)	5	2.80(1.76-4.45)	4	4.00(2.33-6.88)	7	1.37(0.89-2.11)	16	1.00(0.68-1.48)

N/A = not reported

Comparison of outcomes between different ADMs

There are no studies directly comparing one ADM versus another, however there are reports on outcomes using a specific ADM. Exploratory analysis from the iBRA study, a non-randomised multi-centre prospective cohort study (n=2655 immediate implant based reconstructions), showed no association between the 14 different biological xenografts and synthetic meshes used and short-term outcomes (205).

1.4.7 Aesthetic outcomes in ADM-assisted immediate implant-based reconstruction

There are currently four published studies (63, 77, 206, 231, 232) comparing the aesthetic outcomes of ADM assisted versus submuscular breast reconstruction. They are all retrospective reviews of photographs by a blinded panel of assessors, ranging from consultants to lay people. Photographs were taken a minimum of 90 days (232) or 12 months (63), at a mean of 1.7 years (231) and an unknown time (206), from the final reconstruction. Each used a different 'established' scale, highlighting the absence of a standardized tool. Overall improved aesthetic outcomes were found with the use of ADMs. Aesthetic outcome deteriorates with time in immediate implant based reconstruction (without the use of ADM) as demonstrated in a study of 364 patients (Figure 10). An acceptable cosmetic result was found in 86% of cases at 24 months compared to 54% at 60 months (233). There are no studies quantifying changes in aesthetic outcome over time in ADM-assisted breast reconstruction. Although capsular contracture plays a role in aesthetic outcome, it is not assessed in combination or correlated with the aesthetic outcome in the four studies. One study used a patient phone survey (77) however did not demonstrate any difference between the two groups in patient reported satisfaction with aesthetic outcome.

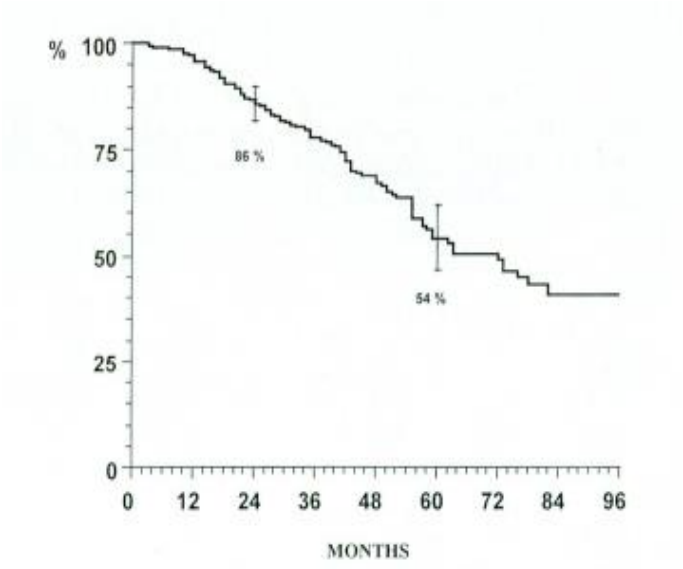


Figure 10 The actuarial percentage of acceptable cosmetic outcome in a study of 364 patients, who underwent implant based breast reconstruction, assessed by a surgeon and two independent assessors (233).

1.4.8 Patient reported outcomes in ADM-assisted immediate implant-based breast reconstruction

There has been 1 RCT (67) comparing patient reported outcomes (PROs) using the BREAST-Q Physical Well-Being: Chest and Upper Body scale pre-operatively, immediately post-operatively, during the expansion phase and before the expander-implant exchange in two-stage expander/implant reconstruction, with (n=36) and without the use of ADMs (n=33). This found no difference between the two groups. The study closed early only recruiting 66% of the target. A retrospective comparative study did not report any significant differences in patient satisfaction between ADM-assisted and submuscular coverage in a telephone survey based on a previously validated questionnaire (66, 77). With patient numbers of only 16 and 18 respectively and a significant difference in time from the procedure to the telephone call between the two groups (10.2 vs. 20.7 months), reduces the quality of the data. It was not stated who made the telephone call, a factor which may introduce bias. A further comparative study with 31 ADM-assisted and 45 submuscular reconstructions, using Breast Q at one year showed no significant difference between patient satisfaction, psychological or physical well-being. Three case series (64, 65, 76) focusing on PROs concluded there is high satisfaction with ADM use. Unfortunately, the mean time from surgery to the reporting of the outcomes is short (6 weeks to 22 months) and the groups were small (16-67). Only two studies assessed PROs at more than one time point (65, 67). No significant difference in physical well-being scores at any of the time points up to complete expansion was found in one study (67). However in the other, Breast Q scores increased i.e. an improvement, between the two and six month time points, at which point they had returned to the pre-operative values in all domains except physical well-being (65). In nine studies comparing PROs in implant only reconstruction with autologous (71, 73, 79-84, 234); lower satisfaction was found in the tissue expansion/implant group. Despite varied patient satisfaction between reconstructive type, patients would still choose the same form of reconstruction again and recommend that type to a friend (79). There are no studies comparing ADM assisted reconstruction with autologous reconstruction published in the literature. Anecdotal evidence suggests other factors such as bigger breast size post-operatively compared to pre-operatively (72) and bilateral reconstruction (82) can improve PROs.

1.4.9 Current clinical trials in ADM-assisted breast reconstruction

A multi-centre randomised controlled trial comparing HADM-assisted one stage implant based reconstruction and two stage expander/implant reconstructions is on-going in Canada (MCCAT) (235). The primary outcome is to assess the mean change in patient satisfaction and quality of life using BREAST-Q between the two groups from baseline to 12 months post reconstruction. Secondary outcomes are change in BREAST-Q score over time, short and long-term complication rates, aesthetic outcomes and cost-effectiveness of using HADM. Despite aiming to assess long-term aesthetic outcomes and complication rates it is only performing the assessments up to 12 months. The complications data is being collected by the investigating surgeon at the postoperative clinic visits, introducing bias. However, the aesthetic result will be evaluated by a panel of three independent blinded observers. A European RCT has ended recruitment early due to increase complications in one group. They are comparing ADM-assisted one stage implant based reconstruction and total submuscular expander/implant based reconstruction using Strattice™, a porcine derived ADM (236).

This is more commonly used in the UK and will hopefully provide more relevant results to our population. Their primary outcome is number of unplanned surgeries and total number of surgeries. Secondary outcomes include aesthetic outcome, complications, quality of life, cost-benefit analysis and breast sensation. Follow-up is longer, continuing to 24 and 36 months but again a relatively short time period from initial reconstruction to gain a good understanding of any long-term benefits compared to traditional methods.

1.5 Capsular contracture in implant-based breast reconstruction with acellular dermal matrices

Implant based breast reconstruction is currently the commonest form of reconstruction performed (21). The major long-term problem with implant-based surgery is capsular contracture, requiring further procedures to correct. There is a recognised need to develop techniques or technologies to minimise this. As anecdotal clinical evidence suggested that ADMs are associated with reduced rates of capsular contracture (207), and minimal capsule formation around the tissue expander and AlloDerm® interface had been witnessed at exchange (237), ADMs are proposed as a preventative measure and are being increasingly used in implant based reconstruction and augmentation (203, 204, 238). The exact mechanism behind this is unclear. One theory is ADMs are closer in composition to a patient's own tissue compared to the implant shell, which initiates a foreign body response when implanted; by forming a barrier between the implant and patient's natural tissues the ADM may inhibit the foreign body reaction which plays a major role in the pathogenesis of capsular contracture. Another possibility is that the topographical features of ADM positively influence the initial cell response in the foreign body reaction reducing the severity of the reaction and therefore the fibrous capsule formation.

1.5.1 Histological findings in studies investigating capsular contracture in ADM-assisted breast reconstruction

In-vitro Studies

Preliminary studies seeding macrophages on to wound ADMs have demonstrated that biomaterials influence the microenvironment to affect macrophage phenotype (239). Macrophages play a key role in the foreign body response and switch from a pro-inflammatory to anti-inflammatory phenotype during the later stages of repair after injury. The down regulation of M2a phenotype macrophage and up regulation of M2c was demonstrated with xenogenic and human ADMs respectively, which could suppress fibrosis (239). Human acellular dermal matrices can affect the levels of inflammatory cytokine and endothelial growth factor expression from macrophages which can impact on the inflammatory response, integration of these products and appropriate wound healing (219). Dysregulation of cellular expression can result in an excessive inflammatory response which can lead to excessive scarring. Expression levels of cytokines (IL-1β, IL-6, IL-8 and VEGF) known to have important functions necessary for proper wound healing were used as markers of macrophage activation when seeded onto human ADMs and a biological mesh. Expression levels varied between products in-vitro but were not correlated with in-vivo performance (219).

Chemically cross-linked porcine acellular collagen matrices induced significantly higher inflammatory cytokines compared to non-cross-linked ADMs (240). They also induced a pro-inflammatory macrophage phenotype which can result in chronic inflammation and fibrosis compared to the non-cross-linked which induced an anti-inflammatory phenotype (220). There are no breast specific in-vitro studies involving ADMs. Kyle et al. produced biomimetic silicone surfaces, replicating micro and nanoscale features of ADM and studied the effects these have on breast derived fibroblasts compared to commercially available silicone implant surfaces. The ADM surface significantly promoted cell adhesion, proliferation and survival as well as inducing a significantly reduced inflammatory cytokine response and down regulation of pro-inflammatory/pro-fibrotic genes (IL8, TNFα, TGFß1 and HSP60)(120).

In-vivo Studies

In animal models significantly thinner capsules with less myofibroblasts are seen around implants covered with AlloDerm® (human acellular dermal matrix) (237, 241) and Strattice™ (242) compared to bare implants, explanted at 10-12 weeks. Reduced inflammation and proliferation rate was also seen when ADM was used (242). Although analysis was carried out in a blinded manner, these studies were largely exploratory with no justification of sample size (four to ten) and at very short time points since implantation.

Clinical Studies

Four clinical studies taking biopsies at the time of tissue expander (TE) exchange, at and away from the ADM interface, showed significant differences in capsule composition (215, 243-245)(Table 11). The capsule was also significantly thicker in areas where the expander was in direct contact with the pectoralis muscle (246). The comparative studies have all taken biopsies at tissue expander exchange, on average 4-8 months from insertion, a short period from implantation of ADM. Including patients who are undergoing revision surgery which can occur over a more varied time period may give a longitudinal view of capsule composition and assess whether there is a sustained difference and reduction in inflammatory response between the two capsules. Biopsies from the ADM capsule in a study without a control group, showed minimal immune cell response (247). A further two studies have compared ADM and subpectoral capsules with and without irradiation showing lower levels of markers of inflammation, fibrosis and vascularity in the ADM capsule with and without irradiation compared to the subpectoral capsules (153, 248). Both studies also found no difference between the ADM capsules in the irradiated and non-irradiated groups. Expression of TGF-ß1 and PDGF-B was found to be decreased in ADM capsules compared to submuscular capsules in irradiated breasts but no difference in non-irradiated (153). Kyle et al. demonstrated several inflammatory and fibrotic genes that are significantly dysregulated in contracted compared to non-contracted breast capsules and fibroblasts however there are no further studies looking at gene expression in capsules where ADMs have been used (132, 134).

Table 11 Summary of studies comparing capsules at and away from the ADM-tissue interface

	Basu et al. (178) Leong et al. (187)	Gaster et al. (190)	Yu et al. (189)	Chopra et al. (191)
Number of patients	20	12	15	10
Number of capsules	20	17	24	19
Type of collagen matrix	Human dermis	Bovine dermis	Human dermis	Human dermis
Average time after tissue expander insertion (range)	4.4 months (2-10)	7.8 months (2-23)	5.6 months (3-13)	5 months (4-6)
Markers of inflammation	Decreased in ACM capsule**	ACM capsule acellular vs. highly cellular native capsule No other comparisons made	Decreased in ACM capsule**	Decreased in ACM capsule**
Markers of fibrosis	Decreased in ACM capsule**		Decreased in ACM capsule	Not analysed
Markers of vascular proliferation	Decreased in ACM capsule**		Decreased in ACM capsule	Not analysed

**statistically significant p<0.005

1.5.2 Clinical findings in studies investigating capsular contracture in ADM-assisted breast reconstruction

A two institution, two surgeon, case series of over 1500 direct to implant ADM-assisted reconstructions, with mean follow-up 4.7 years, found only 12 reconstructions developed capsular contracture (0.8%), all occurring within the first two years post reconstruction (249). Capsular contracture was detected by the operating surgeon at the patient's routine follow-up appointment. Despite no control arm, it has a large number and the longest follow-up period for a case series, although there is clear potential for bias in the study design. This case series may support the theory that ADMs truly do reduce the incidence of capsular contracture as oppose to delay its occurrence (244, 249), however further long-term follow-up studies are needed to strengthen this theory.

The most up to date meta-analysis (229) included only two arm studies from 2011 onward in an aim to refute previous claims of poor outcomes with the early use of ADMs, shown in previous meta-analyses (225-227). This has been the only meta-analysis to include capsular contracture as an outcome. There was 25% less capsular contracture with ADM when compared with submuscular technique.

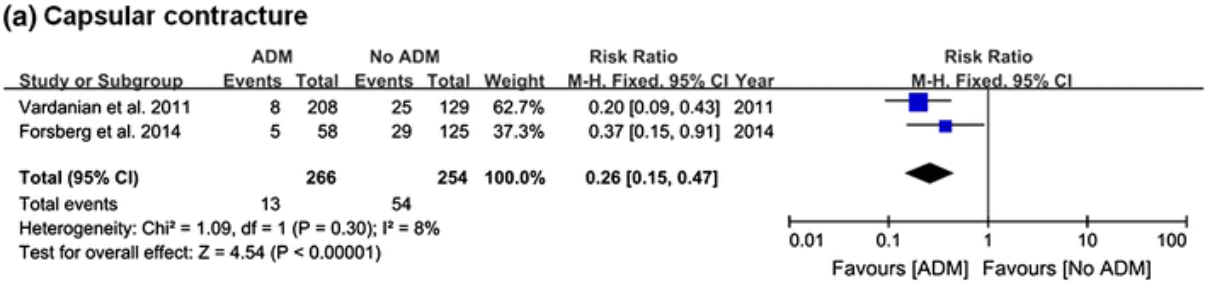


Figure 11 Forest plot estimating the pooled relative risks for capsular contracture in a meta-analysis of two arm studies comparing ADM-assisted breast reconstruction and traditional submuscular technique (229)

Only two studies (63, 206) out of the 23 were suitable to be included for combined analysis for rate of capsular contracture, confirming the lack of evidence detailing this complication. Forsberg et al. (63) retrospectively evaluated consecutive patients who underwent both immediate and delayed breast reconstruction with (n=53) and without ADM (n=125) over a four year period with a minimum follow-up of 1 year, a relatively short time period to pick up cases of capsular contracture. Capsular contracture (grade III or IV) occurred significantly less in the ADM group (8.1% vs. 23.5%, p=0.048). The ADM group had a significantly shorter mean follow-up period than the total submuscular coverage group, 24.6 months compared to 33.8 months. The procedures were performed in a single centre, by four different surgeons however there was no significant difference between them in the frequency of each procedure performed. There was no clarification of who received which type of reconstruction and why; it was likely patient and surgeon choice. This was a chart review therefore it is assumed follow-up was carried out by the operating surgeon, which can introduce bias. Capsular contracture was assessed using Baker grade, however, detection of it in the study will depend on whether it was documented during each visit. Given the retrospective nature follow-up is likely to be incomplete. Vardanian et al. again performed a single centre, retrospective review, although it is unclear as to how many surgeons were involved (206). There were greater numbers undergoing ADM-assisted reconstruction (208 vs. 129) in this cohort and only immediate reconstructions were included. The operating surgeon assessed for capsular contracture using Baker grade, again relying on their documentation of it being present at the follow-up visit. Capsular contracture occurred significantly less in the ADM group (3.8% vs. 19.4%, p<0.001). The assessments were at routine follow-up visits, not at planned time points specific to the study. The mean follow-up was 29 months; however, the different procedures were performed during two different time points (submuscular coverage 2000-2004, ADM-assisted 2004-2008), suggesting the ADM group follow-up may have been shorter.

1.6 Conclusions

Although there are identified risk factors, the exact mechanisms behind capsular contracture following breast reconstruction is unknown. The pain, disfigurement and need for repeated operations cause physical and psychological distress. In an era of increasing survivorship and increase in implant-based reconstruction, there is a need for improved technologies and techniques to prevent capsular contracture. Initial studies conclude that ADMs are associated with capsules containing reduced markers of inflammation and fibrosis and lower rates of clinically detected capsular contracture. Although they appear to be associated with an increase in short term morbidity this may be outweighed by the potential reduction in long-term morbidity and improvement in quality of life and cosmesis. There is a significant lack of high quality evidence when comparing outcomes in implant only versus ADM-assisted breast reconstruction but a randomised control trial to compare long-term outcomes would take many years to complete. As many surgeons and patients have come to the conclusion, despite the controversial evidence available, that ADM assisted reconstruction is preferential the uptake to such a trial may be poor. The majority of publications are reporting outcomes derived from ADM use in the USA where they largely use human derived ADMs consequently it may not be transferable or assumed to be relevant to a UK population where only xenogenic ADMs are available. Therefore, there is a need for high quality data based on the UK practice and population.

1.7 Hypotheses

ADM-assisted implant-based breast reconstruction has reduced incidence of capsular contracture, improved PROs and improved aesthetic outcomes compared to implant only breast reconstruction

The implant capsule at the ADM-tissue interface has a reduced inflammatory response compared to the implant capsule deep to the pectoralis muscle

1.8 Aims

1.8.1 Retrospective clinical cohort study

In a retrospective multicentre cohort study, comparing patients who have undergone immediate ADM-assisted implant-based breast reconstruction with Strattice™ to those who have undergone implant only breast reconstruction with a submuscular technique, the aims are to:

a. Identify the incidence of capsular contracture using Baker grade and tissue tonometry
b. Identify risk factors for capsular contracture
c. Identify the rates of revision surgery
d. Assess patient reported outcome measures (PROMs) using the BreastQ
e. Assess aethetic outcome using photographs and a blinded panel of assessors

1.8.2 Prospective tissue biopsy study

In patients undergoing revision surgery after ADM-assisted subpectoral implant-based breast reconstruction, the aims are to:

a. Compare the capsule composition at the ADM-tissue interface with the capsule deep to the pectoralis muscle
b. Assess whether the presence of ADM reduces levels of inflammatory biomarkers involved in fibrosis within the implant capsule at the ADM-tissue interface compared to the capsule deep to pectoralis muscle

2. Methods

2.1 Breast Reconstruction With and without StratticE (BROWSE)

A multi-centre, retrospective cohort study comparing patients who underwent immediate Strattice™-assisted breast reconstruction with a submuscular technique.

2.1.1 Retrospective study – comparing short and long-term clinical outcomes in Strattice™-assisted and submuscular reconstructions

Identification of patients

Participants were identified from the operating theatre electronic database and theatre and implant insertion log books that prospectively record every breast implant placed within a hospital. This was then cross referenced with coding, consultant operating logbooks and prospective databases of reconstructions.

Consecutive patients who underwent immediate implant based breast reconstruction with a Strattice™-assisted or submuscular technique between 1st January 2009 and 31st December 2015 at either Wythenshawe Hospital (MFT) in Manchester, Royal Victoria Infirmary (RVI) in Newcastle or Bradford Royal Infirmary (BRI) were included.

Data collection

A retrospective case note review was performed. Clinic letters, MDT outcomes, operation notes, anaesthetic charts, admission pathways, nursing notes, histology and radiology reports and all handwritten clinical documentation were reviewed. Data was collected on a case report form (Appendix 7.3) including patient demographics, operative technique, adjuvant treatment, post-operative complications and further surgery.

Definitions

The following definitions were used when compiling the data. They were adapted from the definitions used in the iBRA study, a UK multicentre prospective cohort study of implant based breast reconstruction to allow for a more meaningful comparison (250).

Suspected infection – clinical signs within the breast; hot, erythema, swelling, purulent discharge and/or systemic signs e.g. fever

- **Minor** – requiring oral antibiotics only
- **Major 1** – requiring admission for IV antibiotics
- **Major 2** – requiring surgical drainage/debridement

Wound dehiscence – separation of the skin edges at the wound site

- **Minor** – treated conservatively or with a minor procedure in clinic
- **Major** – requiring return to theatre for re-suturing under general anaesthetic

Seroma – a collection of serous fluid under the wound/around the implant which, if symptomatic may require draining through needle aspiration

Haematoma – collection of blood beneath the incision/around the implant

Unplanned explantation – implant removal due to infection/wound problems, cosmesis or other reasons that was not part of the initial planned reconstructive procedure. It may or may not have been replaced.

Planned further surgery – surgery that was planned as part of the overall reconstructive procedure e.g. TE to definitive implant, nipple reconstruction, port removal or contralateral surgery

Unplanned further surgery – surgery that is required due to a complication of or problem with the initially performed reconstruction. Whether emergency or elective, it was not an anticipated step of the overall reconstructive procedure.

Long-term complications requiring revision surgery

Data was captured from retrospective notes on the reasons for further surgery therefore definitions were not created specifically for this study. The reasons for revision surgery collected for the purpose of this study were; capsular contracture, malposition, asymmetry, rupture, contour defects, rippling, animation, patient request to change style or size and other. These are all classified as major complications due to the need for surgical intervention. Given the retrospective nature of the study it is not possible to ascertain from the hospital records the rate or severity of minor complications.

Statistical methodology

Chi-squared or Fisher's exact test was used to compare nominal variables. Independent samples t-test and Mann-Whitney U test was used to assess the difference in means of the continuous variables. Statistical tests were performed using SPSS 22.0 for windows (SPSS Inc, Chicago, Illinois, USA).

2.1.2 Clinical cohort Study - assessing rates of capsular contracture, aesthetic and patient reported outcomes in Strattice™-assisted and submuscular reconstructions

Approvals

The study was reviewed by North West Research Ethics Committee (16/NW/0082) and favourable opinion given on 4th April 2016. Due to a change in policy a request was submitted to bring the study under Health Research Authority (HRA) approval and this was given on 4th August 2016.

Funding

This study was funded by Allergan plc but they played no role in the conduct of the study or analysis of the results.

Inclusion and exclusion criteria

Female patients 18 years or older, who had undergone immediate implant-based reconstruction with or without Strattice™ from January 2009 to December 2015 with a minimum of six months follow-up who understood written English and were able to give consent. Exclusion criteria include any dermal sling, autologous or delayed reconstruction.

Primary Outcome

Incidence of capsular contracture, measured at a single time point in the follow-up period when the patient attended for clinical examination. Defined as a Baker III or IV capsule (164).

Secondary Outcomes

Quality of life assessed using the BREAST-Q at a single time point in the follow-up period.
Aesthetic assessment by a blinded panel of three assessors using three view photographs taken at a single time-point during the follow-up

Recruitment

Participants identified for the retrospective study were confirmed as eligible for this study if they were alive with an implant-based reconstruction and were invited to participate via post. (Appendix 7.1 and 7.2) (Figure 12)

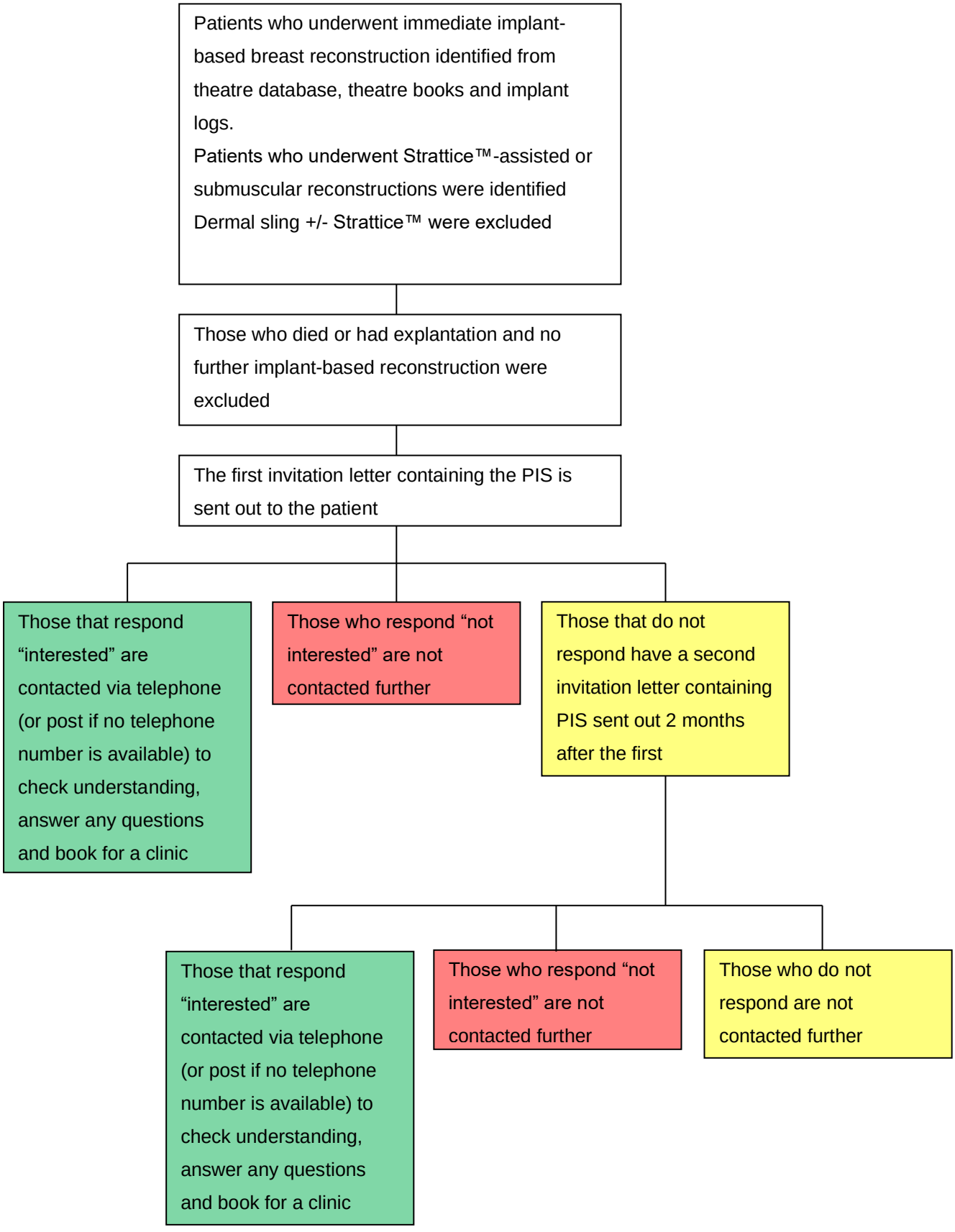


Figure 12 Recruitment pathway for BROWSE Study

Assessment of capsular contracture

Patients attended a clinic appointment to consent to the study and for standard breast examination and tonometry measurements performed by lead researcher, Rebecca Wilson (RW).

Baker grade

RW graded each breast. Participants were also asked to grade their breasts using the classification below

I The breast is normally soft and looks natural

II The breast is a little firm but looks normal

III The breast is firm and looks abnormal

IV The breast is hard, painful and looks abnormal

Tonometry

Tonometry was performed in each quadrant of the breast using the Flinders Tissue Tonometer model BME1428 (manufactured by Flinders Medical Centre, South Australia), figure 13a. The device provides a constant force via a 200g weight, exerting a pressure of 29.6 kg/cm$_2$ at the end of the 1mm diameter plunger. The device is held perpendicular to the breast (Figure 13b), ensuring the bubble is within the circle (Figure 13c) then placed on the breast and a reading (0-10) is taken from the dial. An average score per breast was calculated using the four quadrant readings.

a.

b. **c.**

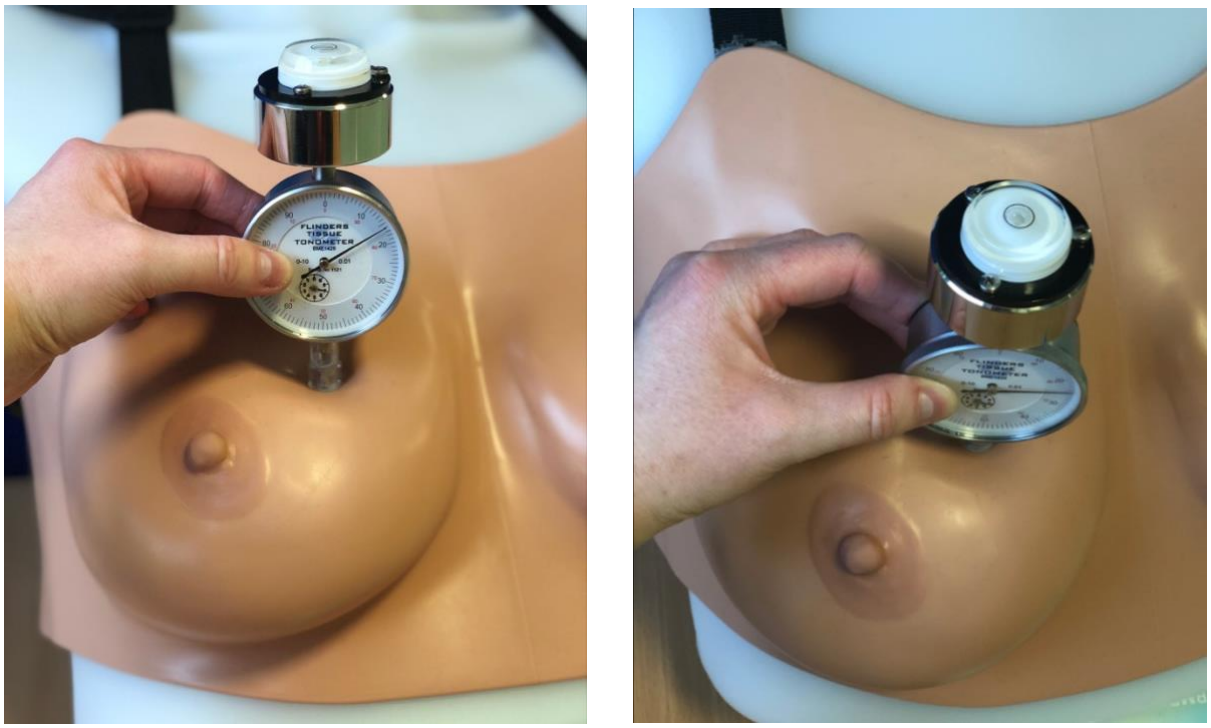


Figure 13a-c Flinders Tissue tonometer

Evaluation of aesthetic outcome

Participants attended medical illustration department for photographs following the study standard operating procedure (Appendix 7.4). This was designed so that all participants were photographed using a standard and reproducible technique so that photographs could be compared anonymously. The photographs were securely stored on a NHS level encrypted device until the end of the study then a PowerPoint presentation containing the three views (front, left and right lateral) of all participants to be rated was created. The photographs were randomly assigned in order of study number. Internal controls were placed within the presentation to assess intra-operator reliability. Independent panel members were chosen who had no prior knowledge of the study. The blind panel consisted of a breast surgeon, breast care nurse and lay person. They were trained on the use of the PowerPoint program and the scoring scale, where a score of one to ten was given for overall satisfaction and score of one to five in each domain (Table 12) (Appendix 7.5).

Table 12 10-point scale used in the assessment of aesthetic outcomes after breast reconstruction by Visser et al. (62)

Characteristic	Scale
Breast volume	1 (very dissatisfied) ----------2----------3----------4---------- 5 (very satisfied)
Breast shape	
Breast symmetry	
Breast scars	
Nipple/NAC	
General satisfaction	1 (extremely dissatisfied) --2--3--4--5--6--7--8--9--10 (extremely satisfied)

Quality of Life

Participants were given the Breast-Q: post-operative reconstruction module (Appendix 7.6) during the clinic visit. They were asked to fill this out in their own time, not in the presence of the researcher and return it in the envelope provided.

Sample size and power calculation

Using the average estimated rate of capsular contracture at six to ten years in submuscular reconstructions of 15% -25% (155, 160) and 6% (63, 206) in ADM-assisted reconstructions, the sample size required to have 80% power to detect a difference at the 2-sided 5% significance is 125 reconstructions in the Strattice™-assisted group and 63 in the submuscular group, based on a chi-squared test.

Statistical methodology

Chi-square or Fisher's exact test was used to compare nominal variables. Independent samples t-test and Mann-Whitney U test was used to assess the difference in means of the continuous variables. Intraclass correlation coefficient was used to analyse reliability. Pearson's correlation coefficient was used to assess association between variables. Statistical tests were performed using SPSS 22.0 for windows (SPSS Inc, Chicago, Illinois, USA).

2.2 Capsule Study – a comparison of capsule in patients undergoing subpectoral breast reconstruction with implant and porcine acellular dermal matrix

A comparison of markers of fibrosis and inflammation, using histology and immunohistochemistry, present in implant capsules which were in contact with (ADM capsule) and away from (native capsule) Strattice™ after subpectoral Strattice™-assisted breast reconstruction.

All laboratory work was performed by lead researcher (RW) unless otherwise specified e.g. where an automated machine was used, after appropriate training from other members of the Bayat Laboratory Group. RW was present for and taught aspects of the histopathological analysis performed by Dr Susan Pritchard.

2.2.1 Approvals

A regional ethics application was prepared and submitted in line with new HRA guidelines by lead researcher (RW). The study was reviewed by North West Research Ethics Committee (16/NW/0373) and favourable opinion given on 14th June 2016, followed by HRA approval on 19th July 2016. Trust R&D approval was granted on 10th January 2017.

2.2.2 Inclusion and exclusion criteria

Patients 18 years or older, undergoing revision surgery following subpectoral Strattice™-assisted breast reconstruction capable of providing informed consent were eligible to participate in the study. Exclusion criteria included, patients undergoing revision surgery following any other type of breast reconstruction and patients with known active or chronic infections e.g. Hepatitis C, HIV.

2.2.3 Patient recruitment

Patients undergoing revision surgery after Strattice™-assisted breast reconstruction were identified from the Oncoplastic MDT and Surgeon theatre diaries at Wythenshawe Hospital. They were approached by the clinical team and if interested given a participant information sheet (Appendix 7.6). RW followed-up interested patients with a telephone call and if they were willing, recruited them to the study.

2.2.4 Clinical Assessment

Prior to the revision surgery the participant was examined to assess Baker grade and tonometry was performed as previously described. Demographics and baseline clinical data was collected (Appendix 7.8).

2.2.5 Sample collection

During the revision procedure, the operating surgeon took four biopsies from two areas of the capsule using a 5mm punch biopsy, where this was not possible, a free hand biopsy was taken. Two biopsies were taken from i) the inferior pole of the reconstruction, the site of previous Strattice™ placement and ii) the upper pole of the reconstruction, in an area away from the Strattice™ and deep to the pectoral muscle. These were immediately placed in to 10% neutral buffered formalin solution (Sigma Aldrich, UK) and RNA-later (Ambion, USA), one each per site and transported to the Institute of Inflammation and Repair at the University of Manchester where they were stored at 4ºC (formalin) and -80ºC (RNA-later).

2.2.6 Tissue preparation

Tissue samples were fixed in 10% neutral buffered formalin solution (Sigma Aldrich, UK) for a minimum of 48 hours before being placed into labelled cassettes and processed by an automated tissue processor (Leica, UK). The samples are sequentially submerged as follows:

Step	Solution	Time (hrs:mins)
1	70% alcohol	00:20
2	70% alcohol	00:30
3	90% alcohol	00:45
4	90% alcohol	01:00
5	100% alcohol	00:30
6	100% alcohol	00:45
7	100% alcohol	01:00
8	xylene	00:20
9	xylene	00:30
10	xylene	00:40
11	wax	01:10
12	wax	01:10
13	wax	01:10

Cassettes were removed from the processor and placed on a paraffin embedding hot plate set at 60°C. Samples were removed from the cassettes and placed into a pre-heated wax block mould. Molten paraffin (Leica, UK) was poured over the tissue sample and left to set on a cold plate.

The tissue blocks were removed from the mould. They were cut into 5µm thick sections using a microtome (Leica, UK), placed in to a water bath set at 37°C and mounted on to pre-labelled, charged superfrost plus microscope slides (Thermo Scientific, USA). The slides were left to dry overnight in a 40°C oven then stored at room temperature in a slide box.

2.2.7 Haematoxylin and Eosin (H&E) staining

H&E staining was performed on 24 breast capsules (12 ADM, 12 native) using an automated machine (Leica, UK). The process was as follows:

Step	Solution	Time (minutes)
1	Xylene	2:00
2	Xylene	2:00
3	Ethanol	2:00
4	Ethanol	1:00
5	70% IMS	0:30
6	Running water	1:00
7	Haematoxylin	2:00
8	Running water	1:00
9	5% acetic acid	0:10
10	Running water	1:00
11	Scott's tap water	0:30
12	Running water	1:00
13	Ethanol	1:00
14	Alcoholic eosin	1:30
15	Ethanol	1:30
16	Ethanol	1:30
17	Xylene	2:00
18	Xylene	2:00

2.2.8 Herovici staining

Herovici staining was performed manually on 24 breast capsules (12 ADM, 12 native) following the process below, then mounted using Consul-Mount™ (Thermo Scientific, USA)

Step	Solution	Time (minutes)
1	Xylene	5:00
2	Xylene	2:00
3	100% Ethanol	2:00
4	100% Ethanol	1:00
5	70% Ethanol	1:00
6	Tap water	1:00
7	Staining solution*	4:00
8	1% acetic water	2:00
9	100% Ethanol	2:00
10	100% Ethanol	1:00
11	Xylene	2:00
12	Xylene	2:00

*Staining solution was made up from Van Gieson Solution (HTA254, Sigma Aldrich), Methyl blue 0.05%, glycerol and lithium carbonate

2.2.9 Elastin Van Gieson staining

Elastin Van Gieson staining was performed manually on 24 breast capsules (12 ADM, 12 native) following the process below, then mounted using Consul-Mount™ (Thermo Scientific, USA)

Step	Solution	Time (minutes)
1	Xylene	5:00
2	Xylene	2:00
3	100% Ethanol	2:00
4	100% Ethanol	1:00
5	70% Ethanol	1:00
6	Tap water	1:00
7	Staining solution*	15:00
8	Running tap water	1:00
9	Differentiating solution**	1:00
10	Running tap water	1:00
11	Sodium thiosulphate solution	1:00
12	Running tap water	1:00
13	Van Gieson's solution	5:00
14	95% Ethanol	1:00
15	95% Ethanol	1:00
16	100% Ethanol	2:00
17	100% Ethanol	1:00

*Staining solution was made up from haematoxylin solution 5%, ferric chloride solution 10% and Lugol's iodine solution

**Differentiating solution was made up of ferric chloride 2%

2.2.10 Immunohistochemistry staining

Immunohistochemistry was performed on 24 breast capsules (12 ADM, 12 native) and 1 positive control using primary antibodies outlined in Table 13.

Dewaxing, rehydration and antigen retrieval

Immediately prior to staining the sections were dewaxed and rehydrated by passing the slides through the following:

1. 100% xylene for 10 minutes x2
2. 100% ethanol for 5 minutes x2
3. 90% ethanol for 3 minutes
4. 70% ethanol for 3 minutes
5. Running water for 1 minute

Heat mediated antigen retrieval was performed by heating the slides in a microwave for 20 minutes submerged in citrate buffer (pH 6.0) then leaving to cool for 40 minutes. The slides were then washed in de-ionized water.

Staining

IHC staining was performed with the Novolink™ detection kit RE7150-CE (Lieca, UK), using the following protocol with 2x five minute TBS washes between each step:

1. Peroxidase block for 5 minutes
2. Protein block for 5 minutes
3. Primary antibody overnight
4. Post primary for 30 minutes
5. Novalink polymer for 30 minutes
6. DAB chromogen for 5 minutes
7. Haematoxylin for 5 minutes

The sections were dehydrated following the reverse of the dewaxing and rehydration protocol above then mounted using Consul-Mount™ (Thermo Scientific, USA)

Table 13 Primary antibodies used in the IHC staining of breast capsules

Primary Antibody	Host Species	Antibody details	Retrieval	Dilution	Positive Control
Collagen I	Rabbit	ab34710 (ABCAM)	Proteinase K	1:2000	Skin
Collagen III	Mouse	ab6310 (ABCAM)	Proteinase K	1:2000	Skin
α-SMA	Mouse	A5691 (Sigma-Aldrich)	Proteinase K	1:40	Testes
Fibronectin	Rabbit	ab2413 (ABCAM)	Proteinase K	1:1000	Kidney

Staining validation and optimisation

Each stain was tested at varying concentrations according to manufacturing guidelines and previous experience within the Bayat laboratory group. The test stains were analysed by an independent consultant histopathologist (Dr Miles Howe, Wythenshawe Hospital) to ensure the staining was successful within the capsule tissue and readable. Where necessary adjustment of intensities were made until optimum conditions were met.

2.2.11 Analysis

Blinded analyses were performed by two independent histopathologists (Dr Rebecca McKerrell and Dr Susan Pritchard, senior consultant histopathologist, Wythenshawe Hospital) using light microscopy.

Features analysed with H&E included;

- Fibrosis - eosin (pink) stained stroma was scored on a scale on a scale of 0 (none), 1 (mild density -25%), 2 (moderate density >25% - 75%) and 3 (severe density - >75%), based on the density of fibrous compared to non-fibrous stroma such as fat. Thickness (mm) of the fibrosis was also measured
- Inflammation - the presence of acute (neutrophils) or chronic (lymphocytes, eosinophils, macrophages and multinucleated giant cells) inflammatory cells was scored on a scale of 0 (none), 1 (mild – few scattered inflammatory cells with space between each cell), 2 (moderate – increased numbers of inflammatory cells with some areas of densely packed inflammatory cells but adjacent areas of inflammation having space between the inflammatory cells) and 3 (severe – densely packed inflammatory cells with little intervening stroma between cells)
- Perivascular inflammation - presence of inflammatory cells surrounding blood vessels was also scored on a scale of 0 (none), 1 (mild – few scattered inflammatory cells with space between each cell), 2 (moderate – increased numbers of inflammatory cells with some areas of densely packed inflammatory cells but adjacent areas of inflammation having space between the inflammatory cells) and 3 (severe – densely packed inflammatory cells with little intervening stroma between cells)
- Vascularity - blood vessels were identified as endothelial lined structures containing blood constituents (red blood cells with scattered white blood cells) and manually counted in the two most abundant areas at magnification x20 (0.75mm field diameter). A mean of the two counts was taken per capsule
- Cellularity - Fibroblasts were identified by their classical spindle-like, slim, oval, elongated nuclear features and manually counted in the two most abundant areas at magnification x40 (0.50mm field diameter). A mean of the two counts was taken per capsule
- Synovial-like metaplasia

The elastin van Gieson stain was semi-quantitatively analysed using a score of 0 (none), 1 (occasional elastin fibres with non-elastin stroma between the elastin fibres), 2 (scattered elastin fibres with non-elastin stroma between the elastin fibres), 3 (increased amounts of elastin fibres with occasional areas of densely packed elastin fibres but moderate areas of non-elastin stroma between the elastin fibres), 4 (densely packed elastin fibres with little non-elastin fibres between the elastin fibres).

For the IHC stains a scoring system was used to evaluate the intensity of the stain (0 (none), 1 (weak), 2(moderate), 3 (strong)) and the distribution (0 (none), 1 (patchy), 2 (diffuse)) for Collagen I, Collagen III, and fibronectin. The numerical score was used for statistical analysis. α-SMA was analysed using the percentage stained in the two most abundant areas at magnification x40 (0.50mm field diameter) and a mean was taken per capsule.

There was 85% inter-rater agreement, where there had been disagreement in analysis further review was performed and a consensus taken.

Herovici stain comparing the ratio of mature (collagen I) and immature collagen (collagen III) was analysed using Definiens Tissue Studio. A computer program which was manually pre-trained to detect regions of interest, distinguishing cells and sub cellular objects within these regions (Figure 14). Three samples per capsule were analysed and a mean taken.

a.¶ **b.**

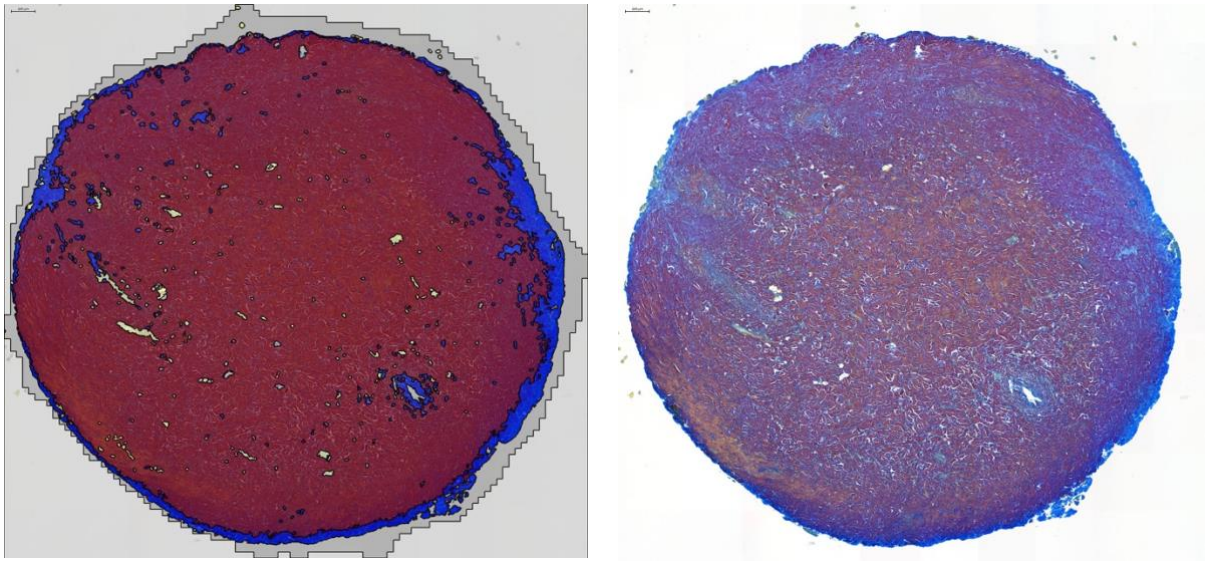


Figure 14 Region of interest training in Definiens Tissue Studio® to identify mature collagen (red), immature collagen (blue), cytoplasm (yellow) **a**. region of interest detection **b**. specimen

2.2.12 Sample size

As this study was exploratory in nature a formal power calculation was not performed. We aimed to recruit ten patients, to allow intra-patient comparison of ten areas of ADM capsule to ten areas of native capsule.

2.2.13 Statistical methodology

McNemar test was used to compare nominal variables. Paired t-test and Wilcoxon signed rank test was used to assess the difference in means of the continuous variables. Statistical tests were performed using SPSS 22.0 for windows (SPSS Inc, Chicago, Illinois, USA).

3. Results: Breast Reconstruction With and without StratticE (BROWSE)

3.1 Retrospective study – comparing short and long-term clinical outcomes in Strattice™-assisted and submuscular reconstructions

3.1.1 Summary of methods

A retrospective case notes review of consecutive patients who underwent immediate implant based breast reconstruction with a Strattice™-assisted or submuscular technique between 1st January 2009 and 31st December 2015 within three tertiary centres.

3.1.2 Demographics of study group

Data was collected for 585 patients across the three tertiary centres. Four patients were excluded due to insufficient data available. 394 patients underwent 553 Strattice™-assisted reconstructions (159 bilateral cases) and 191 patients underwent 242 submuscular reconstructions (51 bilateral cases), five patients had one reconstruction of each type. The median age was 52 years (range 25 - 82) in the Strattice™-assisted group compared to 56 years (range 32-80) in the submuscular group ($p<0.001$). There was a significant number of younger patients and less smokers in the Strattice™-assisted group but no other significant difference in patient demographics and pre-operative risk factors (Table 14). The median follow up was five years and three months (range two years to nine years three months) in the Strattice™-assisted group and five years seven months (range 2 years to 8 years 11 months) in the submuscular group.

3.1.3 Operative data

Centre One performed the largest number of reconstructions, 361 (65.3%) Strattice™-assisted and 209 (86.4%) submuscular reconstructions under the care of 12 surgeons. Centre Two had five surgeons however stopped using Strattice™ in December 2013 and Centre Three five surgeons, however one surgeon performed two thirds of the reconstructions (Figure 15). There was a significantly lower median mastectomy weight in the Strattice™-assisted group ($p=0.0004$) and as expected more simple mastectomies performed ($p<0.0001$) and tissue expanders used ($p<0.0001$) in the in the submuscular group but otherwise no significant differences in comparable surgical techniques between the groups (Table 15). In both groups 99% of patients received peri-operative antibiotics. In the Strattice™-assisted group 98% received a prophylactic course of post-operative antibiotics compared to 93% in the submuscular group.

Table 14 Patient demographics and pre-operative risk factors

	Strattice™-assisted n (%) n=394	Submuscular n (%) n=191	p value
Age (years)			<0.001*
<40	62 (15.7)	11 (5.8)	
40-60	230 (58.4)	108 (56.5)	
>61	102 (25.9)	72 (37.7)	
BMI (kg/m_2)			0.4*
≤17.9	4 (1.0)	6 (3.1)	
18.0-24.9	231 (58.6)	108 (56.5)	
25.0-29.9	115 (29.2)	46 (24.1)	
30.0-34.9	30 (7.6)	24 (12.6)	
≥35.0	11 (2.8)	7 (3.7)	
Unknown	3 (0.8)	0 (0)	
Smoking Status			<0.01**
Smoker	56 (14.2)	46 (24.1)	
Non-smoker	293 (74.3)	133 (69.6)	
Ex-smoker	44 (11.2)	12 (6.3)	
Unknown	1 (0.3)	0 (0)	
Diabetes	9 (2.3)	4 (2.1)	1**
Previous chest wall radiotherapy	16 (4.1)	11 (5.8)	0.36**

*analysis using T-Test

**analysis using Fisher exact and Chi-Square

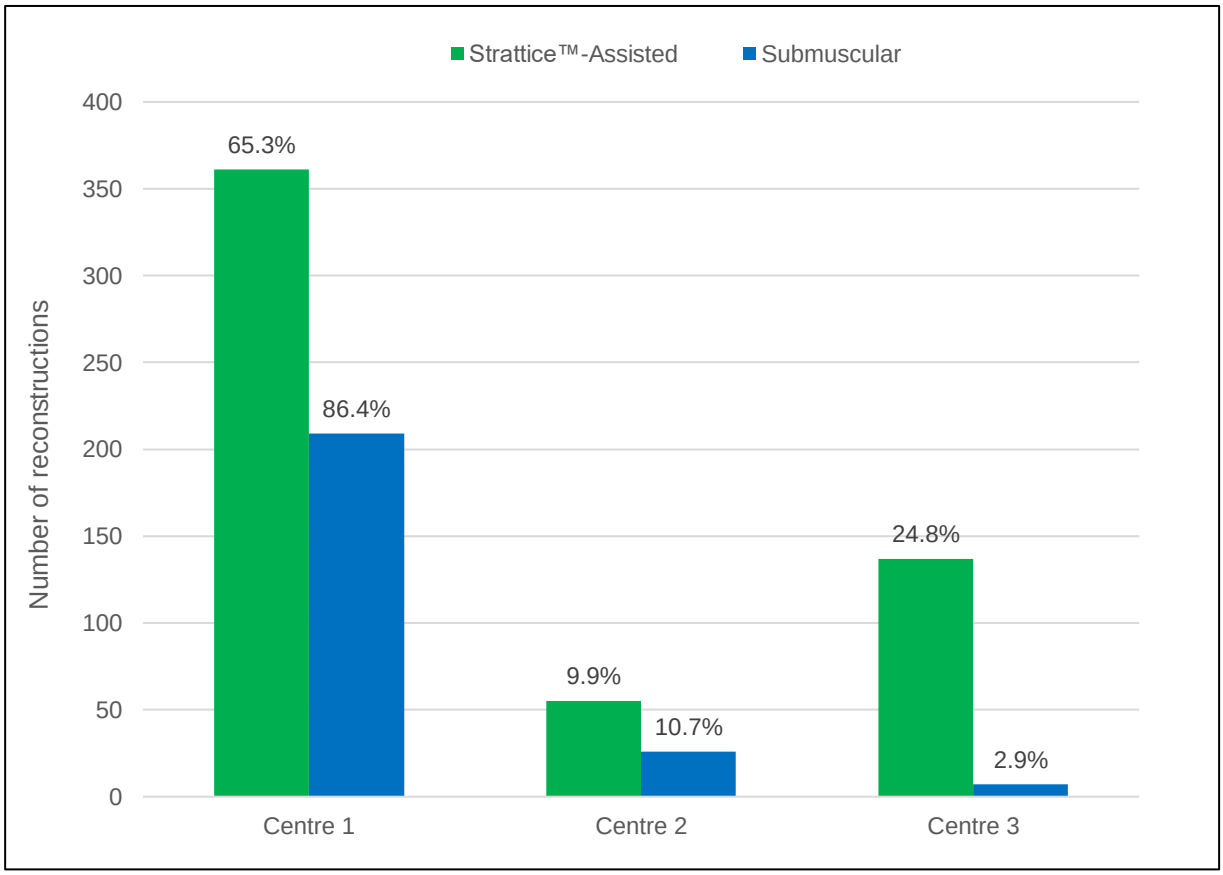


Figure 15 Number of Strattice™-assisted and submuscular reconstructions performed per centre

Table 15 Summary of operative data per breast

	Strattice™-assisted n (%) n=553	Submuscular n (%) n=242
Reason for surgery		
Therapeutic	301 (54.4)	147 (60.7)
Invasive cancer	218 (39.4)	118 (48.8)
In situ carcinoma	83 (15.0)	29 (11.9)
Risk reduction	252 (45.6)	95 (39.3)
Type of Mastectomy		
Skin-sparing (nipple sacrificing)	424 (76.7)	164 (67.8)
Nipple-sparing	119 (21.5)	43 (17.8)
Simple	10 (1.8)	35 (14.4)
Completion mastectomy	94 (17.0)	44 (18.2)
Reconstructive Procedure		
Strattice™ (sub pectoral)	527 (95.3)	0
Strattice™ (pre pectoral)	26 (4.7)	0
Total submuscular	0	199 (82.2)
Partial submuscular	0	37 (15.3)
Subcutaneous	0	6 (2.5)
Incision		
Horizontal	396 (71.6)	152 (62.8)
Vertical	39 (7.1)	26 (10.8)
Lateral	19 (3.4)	3 (1.2)
Wise pattern	14 (2.5)	37 (15.3)
IMF	64 (11.6)	20 (8.3)
Circumareolar	18 (3.3)	3 (1.2)
Other	3 (0.5)	1 (0.4)
Median specimen weight (g) [range]	335 [56 – 1853] [1]	390 [43 – 1897] [2]
Prosthesis		
Tissue expander	74 (13.4)	203 (83.9)
Expander implant	96 (17.4)	20 (8.3)
Implant	383 (69.2)	19 (7.9)
Axillary Procedure		
Nil	274 (49.5)	101 (41.7)
Sentinel Node Biopsy	224[3] (40.5)	118[4] (48.8)
Axillary node sample	3[5] (0.5)	8[6] (3.3)
Axillary node clearance	52[7] (9.4)	38[8] (15.7)

[1]22 not recorded [2]3 not recorded [3]66 were at the WLE or pre-reconstruction [4]16 were at the WLE or pre-reconstruction [5]1 was at the WLE or pre-reconstruction [6]1 was post reconstruction [7]29 were at WLE, pre-reconstruction or post-reconstruction [8]27 were at WLE, pre-reconstruction or post-reconstruction

3.2.4 Post-operative data

There were more T2 tumours (p=0.02) and N2 nodal disease (p=0.05) in the submuscular group but no further significant differences in tumour biology between the two groups (Table 16).

Table 16 Tumour stage comparing Strattice™-assisted and submuscular reconstructions

	Strattice™-assisted n (%) n=553	Submuscular n (%) n=242	p value*
No pathology	234 (42.3)	89 (36.8)	0.14
Tis	91 (16.5)	32 (13.2)	0.25
T1	141 (25.5)	72 (29.8)	0.21
T2	62 (11.2)	42 (9.9)	0.02
T3	12 (2.2)	5 (2.1)	0.93
N0	156 (28.2)	78 (32.2)	0.25
N1	41 (7.4)	26 (10.7)	0.12
N2	7 (1.3)	8 (3.3)	0.05
N3	2 (0.36)	4 (1.7)	0.07
N+	6 (1.1)	2 (0.8)	1
Nx	3 (0.5)	0 (0)	0.56

Where a patient had undergone neo-adjuvant chemotherapy (n=22, Strattice™-assisted and n=7, submuscular) the pre-operative stage was taken.

*Analysis using Fisher exact or Chi-Square

In the Strattice™-assisted group, 316 (57.1%) reconstructions in 288 patients and 153 (63.2%) reconstructions in 150 patients in the submuscular group had malignancy identified on histology. More patients received Herceptin in the submuscular group (11.8% vs. 19.3%, p=0.04), otherwise there was no difference between the two groups in adjuvant therapy received (Table 17).

In the Strattice™-assisted group eight (2.8%) patients had a delay to adjuvant treatment compared to five (3.3%) in the submuscular group.

Table 17 Adjuvant therapy received comparing patients who underwent either Strattice-assisted™ or submuscular reconstruction for the treatment of breast cancer

	Strattice™-assisted n (%) n=288	Submuscular n (%) n=150	p value
Chemotherapy	101 (35.1)*	65 (43.3)**	0.1
Herceptin	34 (11.8)	29 (19.3)	0.04
Endocrine	177 (61.5)	99 (66)	0.4
Radiotherapy	43 (13.5)†	21 (13.7) ††	0.9

*15 (5.2%) and **3 (2%) received chemotherapy after their WLE, before the reconstruction, †Number of reconstruction that received radiotherapy from a total of 316, one was for local recurrence during the follow-up period, †† number of reconstructions that received radiotherapy from a total of 153, one was for local recurrence during the follow-up period.

3.1.5 Post-operative complications

There was no significant difference in the total number of reconstructions that experienced post-operative complications per group. Strattice™-assisted 36.9% (n=204) vs. submuscular 31.8% (n=77), p=0.17. However, more Strattice™-assisted reconstructions were treated for suspected infection and required surgical intervention for wound dehiscence (Table 18 and 19).

Suspected Infection

Suspected infection was recorded if there were any potential clinical signs of infection documented. The total number of reconstructions treated for suspected infection was significantly more in the Strattice™-assisted group (20.6% vs. 12.8%, p=0.009, Table 18). Red breast syndrome described in ADM-assisted reconstructions which mimics signs of infection was documented as the most likely cause of the symptoms in 2.2% (n=12) of the Strattice™-assisted reconstructions but antibiotics were also prescribed. Taking in to account these cases of likely red breast there would be no significant difference in rate of infection between the groups (p=0.06).

In the Strattice™-assisted group 100 patients (25.4%) were treated for suspected infection of whom 36 (36%) had risk factors (13 were smokers and 14 were recent ex-smokers, two were diabetic and 14 had very low or high BMI (7 patients had two risk factors)) whereas in the 294 patients who were not treated for suspected infection 101 (34.4%) patients had risk factors (p=0.77).

In the submuscular group 30 (15.7%) patients were treated for suspected infection, of whom 19 (63.3%) had risk factors (nine were current smokers, one very recent ex-smoker, one diabetic and 11 had very low or high BMI (three patients had two risk factors)) whereas in the 161 patients not treated for suspected infection, 60 (37.3%) patients had risk factors (p=0.007).

Table 18 Rates of suspected infection by treatment type between Strattice™-assisted and submuscular reconstructions

	Strattice™-assisted n (%) n=553	Submuscular n (%) n=242	p value
Treated with oral antibiotics	66 (11.9)[1]	22 (9.1)	0.24
Treated with IV antibiotics	16 (2.9)	3 (1.2)	0.21
Required surgical intervention	30 (5.4)	6 (2.5)	0.07
Total	114 (20.6)	31 (12.8)	0.009

[1] 12 (2.2%) were documented as likely red breast/strattice reaction but given antibiotics in case of mild infection

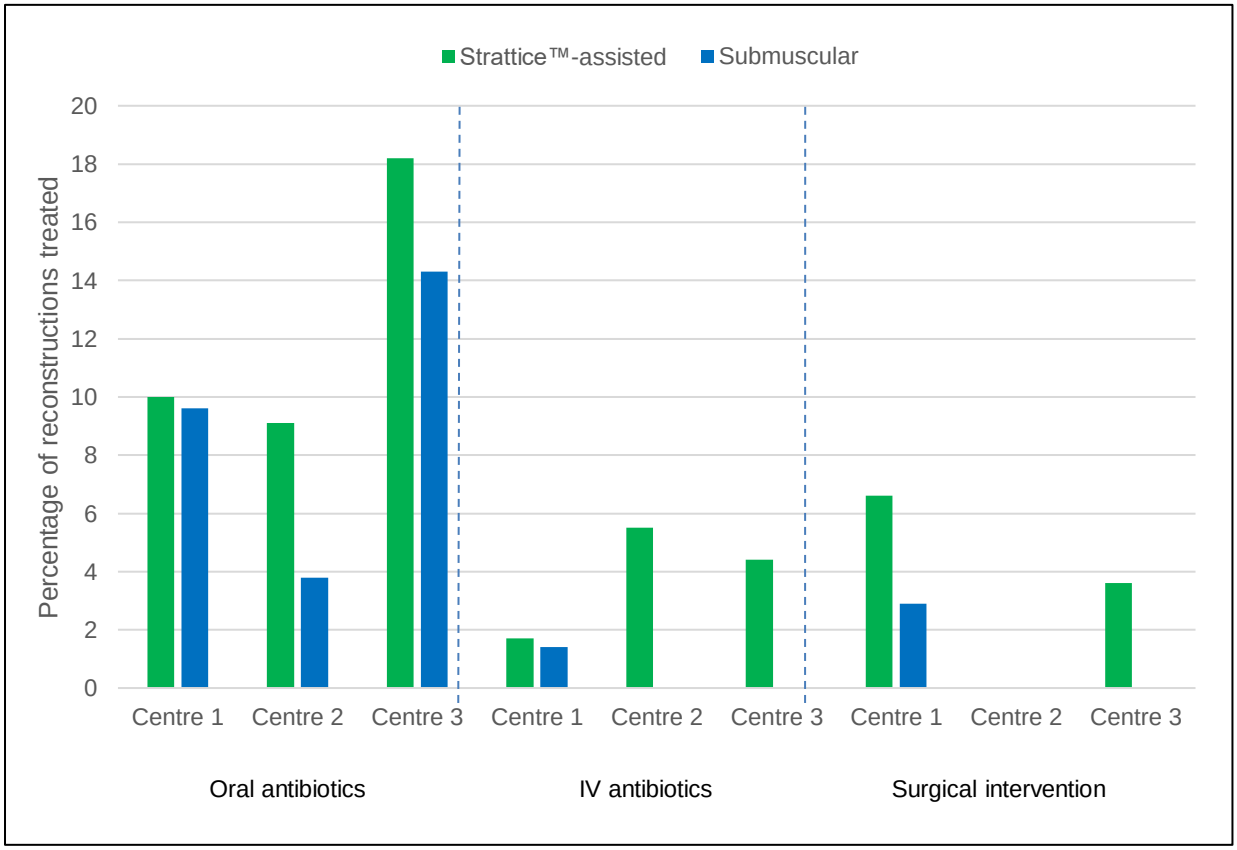


Figure 16 Rates of suspected infection by treatment type between Strattice™-assisted and submuscular reconstructions per centre

Wound dehiscence

Wound dehiscence was recorded if any separation of the skin edges were documented whether intervention was required or not. More strattice™-assisted reconstructions experienced wound dehiscence compared to the submuscular reconstructions (Table 19). There were five (0.9%) reconstructions in the Strattice™-assisted group and four (1.7%) in the submuscular group with documented mastectomy flap necrosis.

In the Strattice™-assisted group 79 patients (20.1%) were treated for wound dehiscence of whom 31 (39.2%) had risk factors (15 were smokers and 8 were recent ex-smokers, two were diabetic and 12 had very low or high BMI (6 patients had two risk factors)) whereas in the 315 patients who were not treated for wound dehiscence 106 (33.7%) patients had risk factors (p=0.35).

In the submuscular group 24 (12.6%) patients were treated for wound dehiscence, of whom 15 (62.5%) had risk factors (11 were current smokers, one very recent ex-smoker, one diabetic and seven had very low or high BMI (five patients had two risk factors)) whereas in the 167 patients not treated for wound dehiscence, 63 (37.7%) patients had risk factors (p=0.02).

Table 19 Rates of wound dehiscence by treatment type between Strattice™-assisted and submuscular reconstructions

	Strattice™-assisted n (%) n=553	Submuscular n (%) n=242	p value
Treated conservatively	31 (5.6)	19 (7.9)	0.23
Required surgical intervention	59 (10.7)	6 (2.5)	<0.001
Total	90 (16.3)	25 (10.4)	0.03

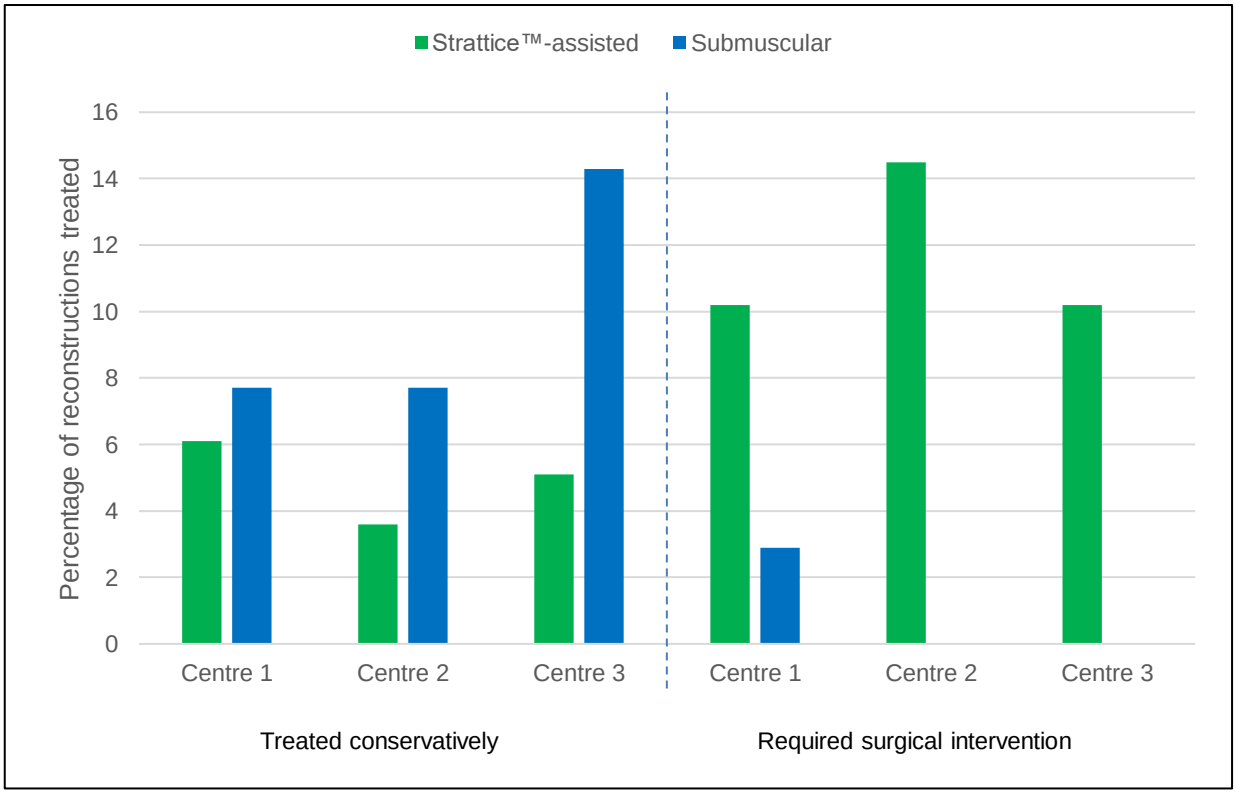


Figure 17 Rates of wound dehiscence by treatment type between Strattice™-assisted and submuscular reconstructions per centre

Seroma

The rates of seroma per reconstruction were equivalent between the two groups however significantly more seromas were aspirated in the submuscular group (Table 20). Of the reconstructions which had aspirations, three (5.4%) in the Strattice™-assisted group had explantation of the implant secondary to infection compared to five (11.4%) in the submuscular group.

Table 20 Rates of seroma comparing Strattice™-assisted and submuscular reconstructions

	Strattice™-assisted n (%) n=553	Submuscular n (%) n=242	p value
Seroma present	129 (23.3)	67 (27.6)	0.19
Seroma aspirated	56 (10.6)	44 (18.1)	0.002
Seroma aspirated >1	22 (4.0)	20 (8.3)	0.13

Return to theatre

More Strattice™-assisted reconstructions required return to theatre to treat wound dehiscence compared to the submuscular group (Table 21) however this did not result in a higher rate of unplanned explantation. Of the 59 Strattice™-assisted reconstructions which required return to theatre to treat wound dehiscence, 32 (54.2%) had explantation of their implant compared to five (83.3%) of six in the submuscular group (p=0.22). Of the remaining 27 Strattice™-assisted reconstructions, eight had the implant exchanged for a tissue expander and two required a second procedure (Figure 18).

Table 21 Reasons for return to theatre in the post-operative period comparing Strattice™-assisted and submuscular reconstructions

	Strattice™-assisted n (%) n=553	Submuscular n (%) n=242	p value
Haematoma	12 (2.2)	3 (1.2)	0.57
Infection	30 (5.4)	6 (2.5)	0.07
Wound dehiscence	59 (10.7)	6 (2.5)	<0.001

Readmission within 30 days

In the Strattice™-assisted group 26 (6.6%) patients were re-admitted to hospital within 30 days compared to 18 (9.4%) in the submuscular group (p=0.12). All but two in each group had problems directly related to the reconstruction. The other reasons for admission were shortness of breath diagnosed with pulmonary embolus (n=1), shortness of breath with normal investigations (n=1), pyelonephritis (n=1) and vomiting (n=1).

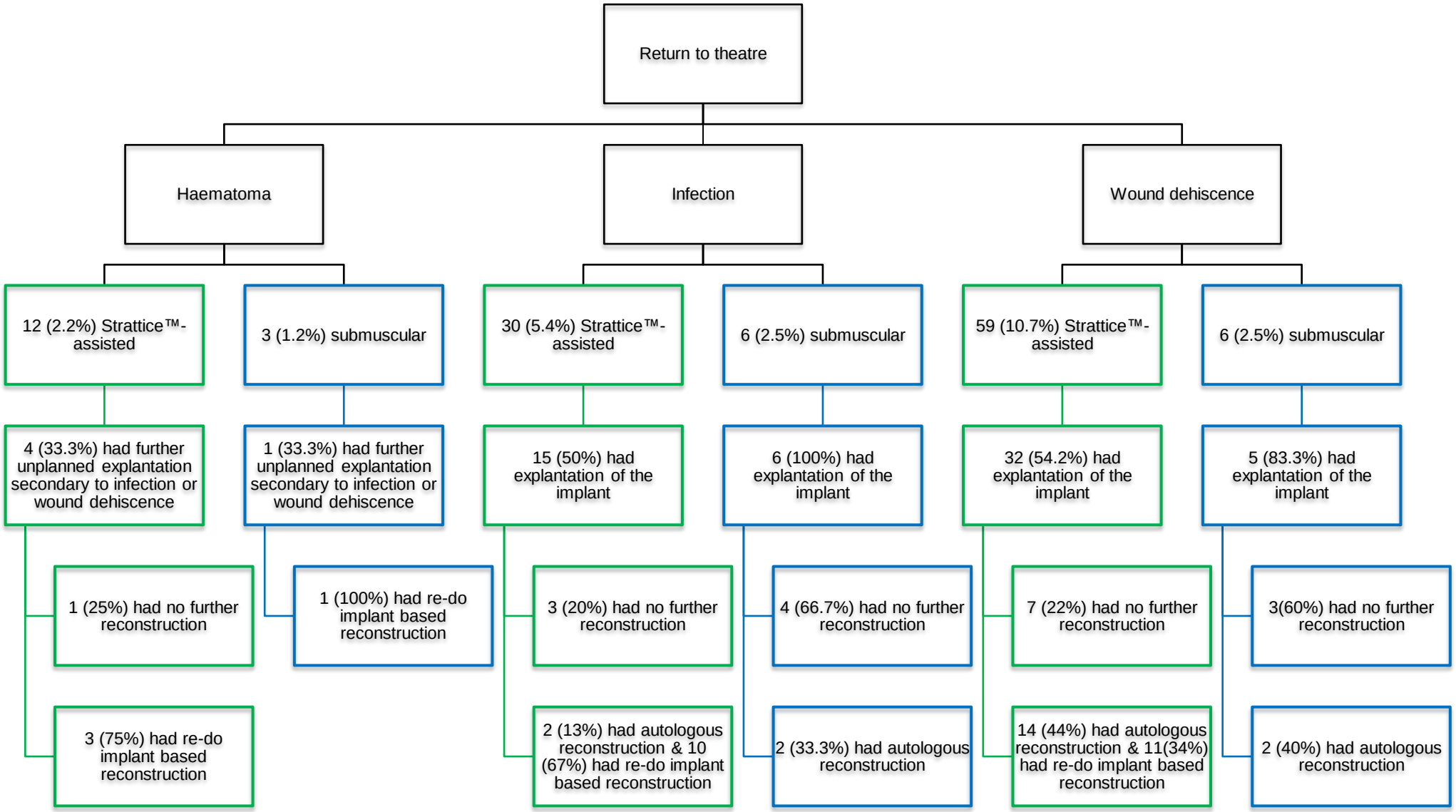


Figure 18 Outcome after return to theatre per complication comparing Strattice™-assisted and submuscular reconstructions

3.1.6 Unplanned explantation

This was classified as implant removal for any reason that was not part of the initial planned reconstructive procedure.

Secondary to post-operative complications

There was no difference in rate of unplanned explantation secondary to post-operative complications i.e. infection or wound dehiscence between Strattice™-assisted (47 of 553, 8.5%) and submuscular (13 of 242, 5.4%) reconstructions (Table 22). In the Strattice™-assisted group 25 (51%) proceeded to further implant based reconstruction (five failed and had autologous reconstruction) and ten (20.4%) to autologous compared to two (15.4%) and three (23.1%) in the submuscular group. In the Strattice™-assisted group 14 (28.6%) had no further reconstruction compared to eight (61.5%) in the submuscular (Figure 18).

In the Strattice™-assisted group 41 patients (10.4%) underwent unplanned explantation secondary to post-operative complications of whom 26 (63.4%) had risk factors (12 were smokers and eight were recent ex-smokers, two were diabetic and nine had very low or high BMI (five patients had two risk factors)) whereas in the 353 patients who did not undergo unplanned explantation secondary to post-operative complications 111 (31.4%) patients had risk factors (p=<0.001).

In the submuscular group 10 (5.2%) patients underwent unplanned explantation secondary to post-operative complications, of whom eight (80%) had risk factors (four were current smokers, two very recent ex-smokers, one diabetic and four had very low or high BMI (three patients had two risk factors)) whereas in the 181 patients who did not undergo unplanned explantation secondary to post-operative complications, 70 (38.7%) patients had risk factors (p=0.01).

Table 22 Unplanned explantation rates between Strattice™-assisted and submuscular reconstructions

	Strattice™-assisted n (%) n=553	Submuscular n (%) n=242	p value
Infection	15 (2.7)	8 (3.3)	
Wound dehiscence	32 (5.8)	5 (2.1)	
Total	47 (8.5)	13 (5.4)	0.12

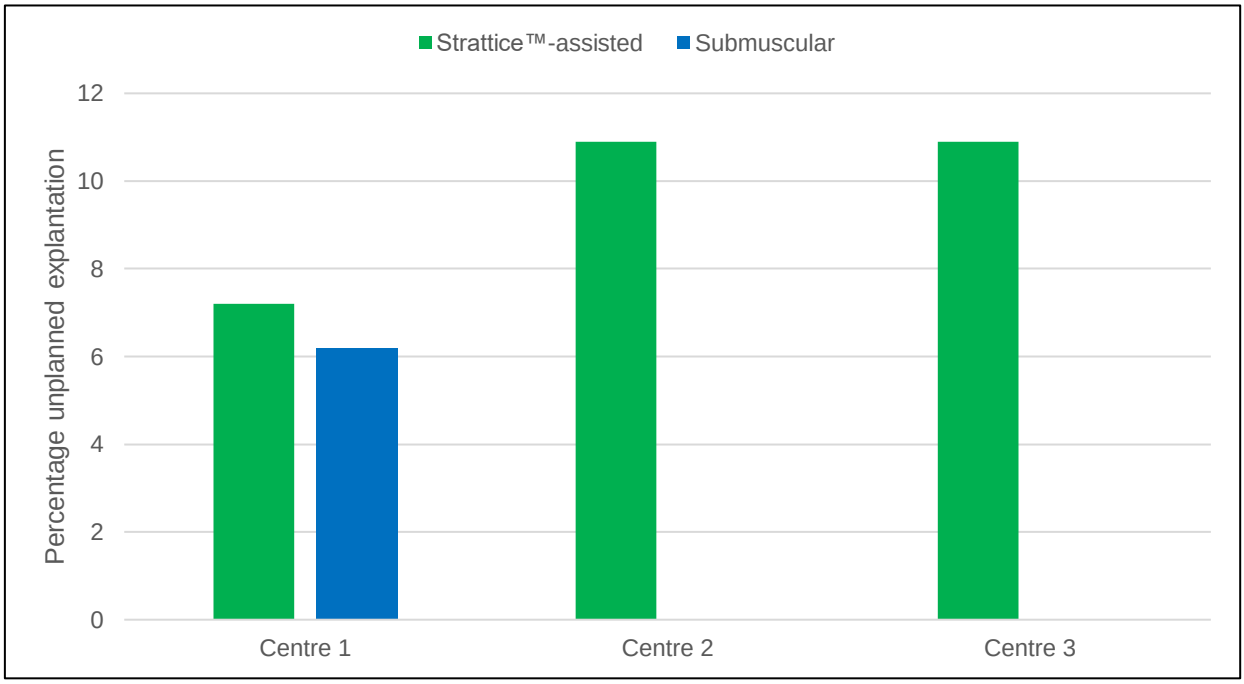


Figure 19 Unplanned explantation rates secondary to post-operative complications between Strattice™-assisted and submuscular reconstructions per centre

Time to explantation secondary to post-operative complications

Median time to explantation was 88 days (range 14-993 days) in the Strattice™-assisted group and 28 days (range 13-225 days) in the submuscular group. Strattice™-assisted reconstructions had a higher explantation rate and the explantations occurred up to almost three years after the reconstruction (log rank test, p=0.04) (Figure 20). Implant loss at 3 months is 4.3% in the Strattice™-assisted reconstructions and 3.7% in the submuscular (Figure 21).

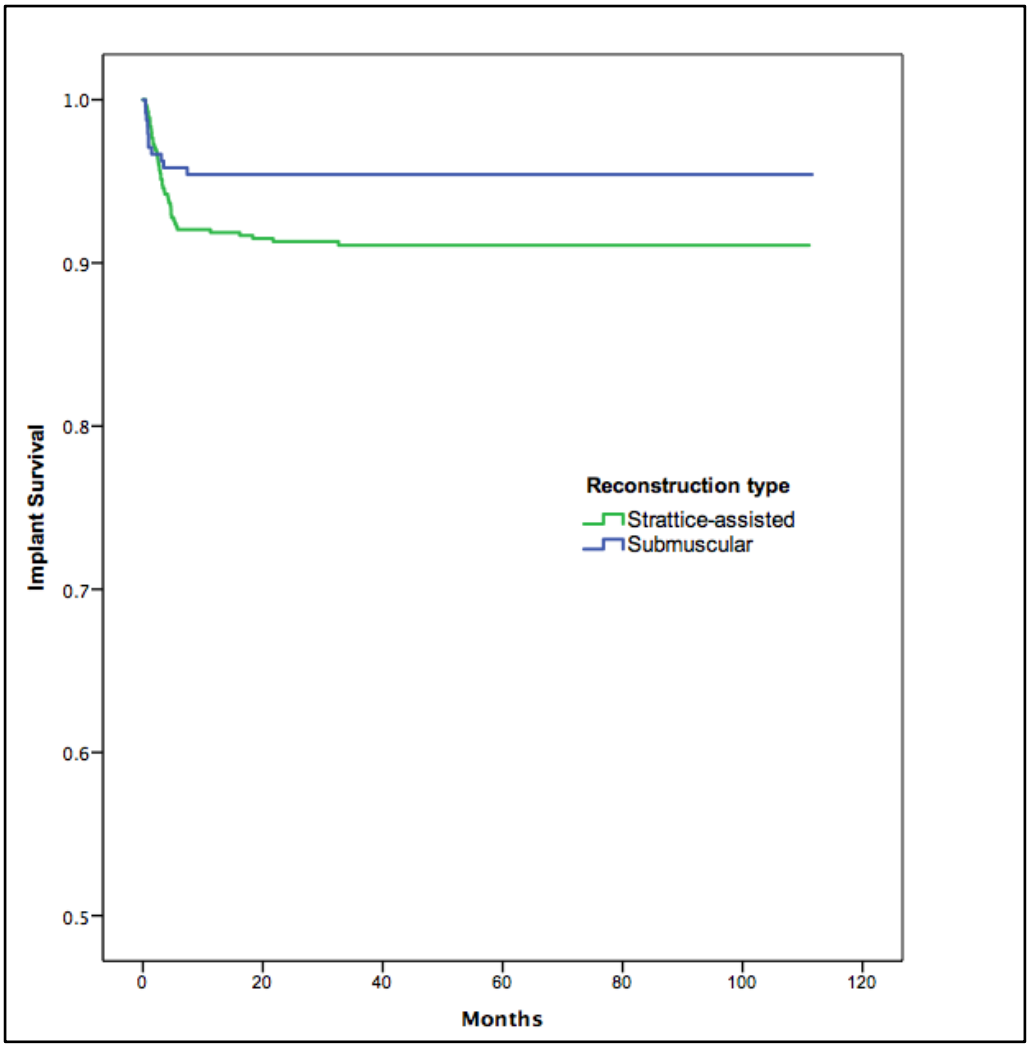


Figure 20 Kaplan Meier curve showing time to unplanned explantation secondary to infection or wound dehiscence following the primary procedure comparing Strattice™-assisted versus submuscular reconstruction

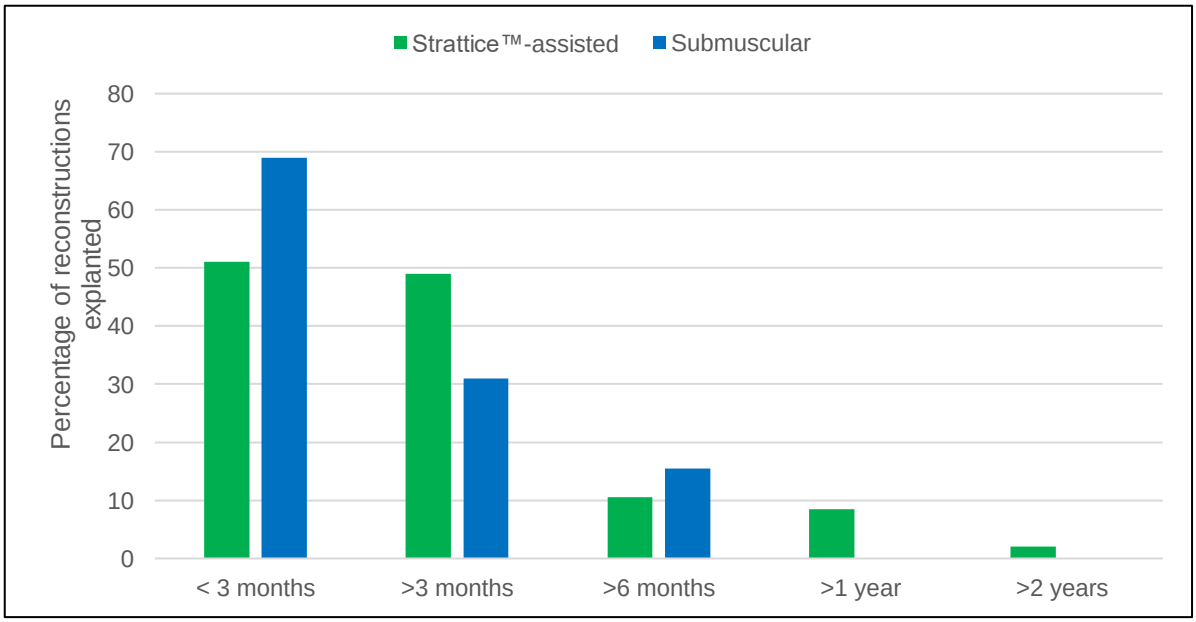


Figure 21 The time to unplanned explantation secondary to infection or wound dehiscence following the primary procedure comparing Strattice™-assisted and submuscular reconstructions

Other reasons for unplanned explantation

We did not demonstrate a difference in the number of, or reason for, unplanned explantation between Strattice™-assisted and submuscular reconstructions (Table 23). 22 (4%) in the Strattice™-assisted group and 13 (5.4%) in the submuscular group (p=0.38) had an unplanned explantation for reasons other than post-operative complications. In the Strattice™-assisted group four (18.2%) had a second attempt at implant based reconstruction, 11 (50%) proceeded to autologous reconstruction and seven (31.8%) had no further reconstruction, compared to zero, eight (61.5%) and five (38.5%) in the submuscular group.

Table 23 Reasons for other unplanned explantation in Strattice™-assisted and submuscular reconstructions

	Strattice™-assisted n (%)	Submuscular n (%)	p value
Pain	0	1	0.3
Radiotherapy damage	1	2	0.22
Capsular contracture	6	6	0.14
Patient preference	2	2	0.59
Complication of further surgery	8	0	0.11
Recurrence	4	0	0.32
Symmetry	1	1	0.52
Recurrent large seroma	0	1	0.3

Time to unplanned explantation for all reasons during follow-up period

During the follow-up period a total of 69 (12.5%) Strattice™-assisted and 26 (10.7%) submuscular implants were explanted with no significant difference in the time to explantations (log rank test p=0.29) (Figure 22).

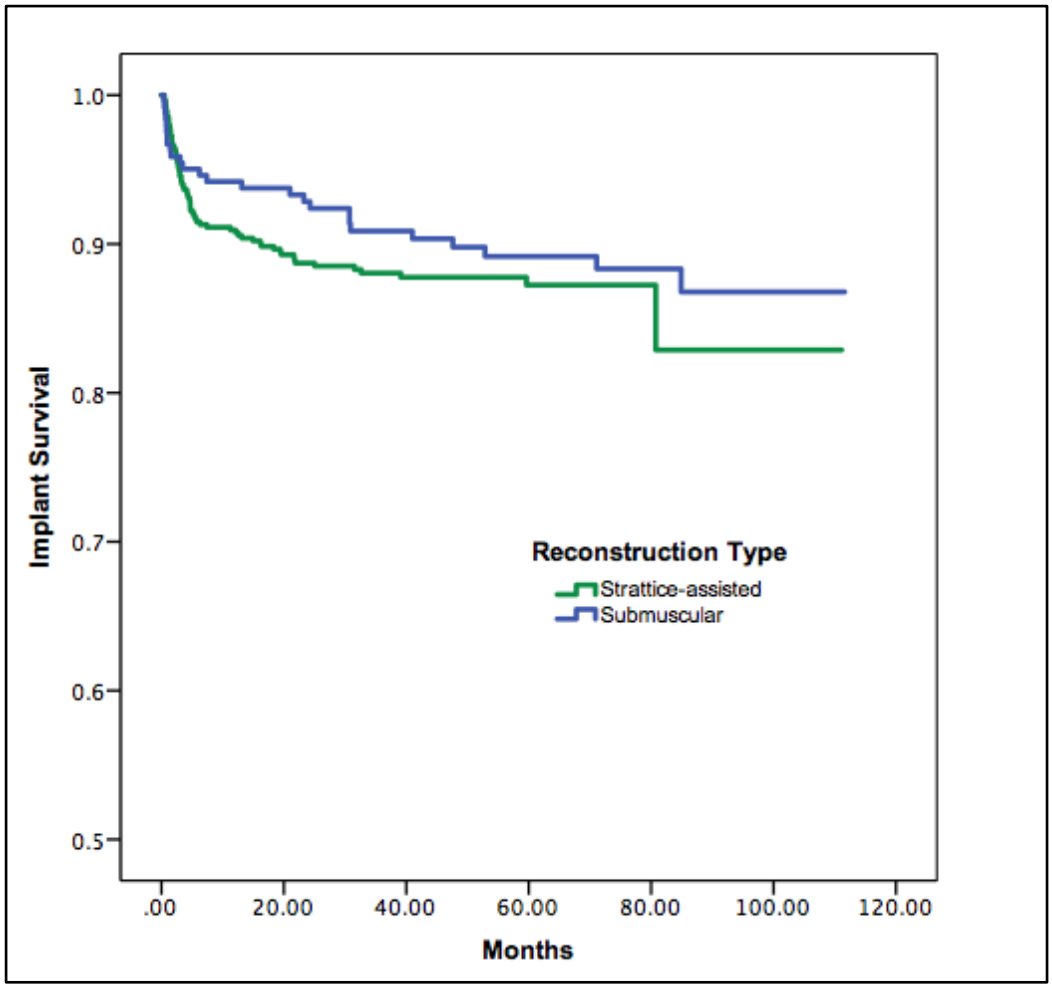


Figure 22 Kaplan Meier curve showing time to unplanned explantation secondary to all causes (post-operative complications & other reasons) comparing Strattice™-assisted versus submuscular reconstruction

3.1.7 Long-term revision rates

For the purpose of this analysis reconstructions with less than 2 years follow-up from completion of the initial reconstructive procedure i.e. when the permanent implant was inserted were excluded (n=84). A further 37 patients (41 reconstructions) were excluded who lost their implant and either had no further reconstruction or had delayed autologous reconstruction. Data for 484 Strattice™-assisted reconstructions in 353 patients (131 bilateral cases) and 192 submuscular reconstructions in 149 patients (43 bilateral cases) were analysed. Median follow-up was 4 year 3 months (range 2 years – 9 years 3 months) in the Strattice™-assisted group and 5 years 7 months (range 2 years – 9 years 3 months) in the submuscular group. There were less smokers in the Strattice™-assisted group but no significant difference in pre-operative risk factors, including BMI, presence of diabetes or previous breast radiotherapy between the two groups.

There was no difference in the number of revisions performed between the two groups during the total follow-up period. 226 (46.7%) Strattice™-assisted reconstructions underwent revision surgery compared to 79 (41.1%) submuscular reconstructions (p=0.19). The revision rate per patient, is 45.3% in the Strattice™-assisted group and 40.3% in the submuscular group (p=0.3).

Analysing only reconstructions with a minimum of five-year follow-up, the revision rate at five years was 55.6% (95 of 171) in the Strattice™-assisted group and 43.3% (55 of 127) in the submuscular (p=0.04).

90 (18.6%) reconstructions underwent more than one revision procedure in the Strattice™-assisted group compared to 32 (16.7%) in the submuscular group.

Revision rates in those who had prior or adjuvant radiotherapy was 32.5% (n=14) in the Strattice™-assisted group, 11.6% (n=5) for capsular contracture and 33.3% (n=5) in the submuscular group, 14.3% (n=3) for capsular contracture.

Time to first revision surgery

Time to first revision was calculated as time from completion of the initial reconstructive procedure i.e. when the permanent implant was inserted. Revisions in the Strattice™-assisted group were performed closer to the initial surgery. Median time to first revision surgery was 11 months (range 1 – 68 months) in the Strattice™-assisted group and 14 months (range 1 – 68 months) in the submuscular group (p<0.001).

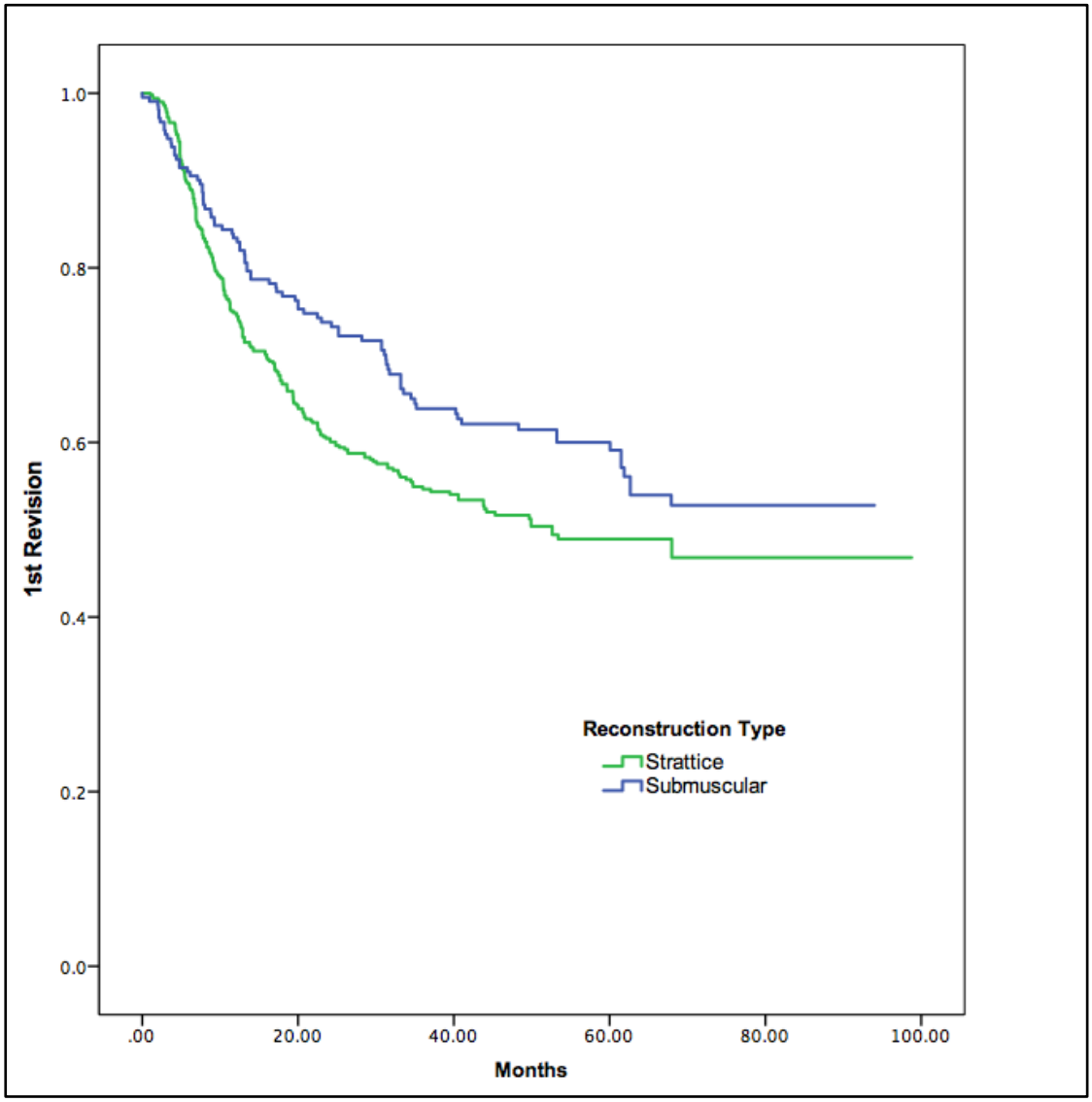


Figure 23 Kaplan Meier curve showing time to first revision comparing Strattice™-assisted and submuscular reconstruction

Reasons for revision surgery

There was a lower revision rate for capsular contracture in the Strattice™-assisted group (Table 24).

Table 24 Reason for revision surgery comparing Strattice™-assisted and submuscular technique

Reason for revision	**Strattice™-assisted n(%) n=399***	**Submuscular n(%) n=141****	**p value**
Capsular contracture	21 (5.3)	22 (15.6)	<0.001
Malposition	24 (6)	5 (3.5)	0.26
Asymmetry	111 (27.8)	42 (29.8)	0.22
Contouring	58 (14.5)	16 (11.3)	0.34
Patient request (size/style change)	53 (11.3)	22 (15.6)	0.49
Rupture	3 (0.8)	1 (0.7)	0.96
Animation	14 (3.5)	4 (2.8)	0.7
Rippling	18 (4.5)	3 (2.1)	0.21
Improve cosmesis	55 (13.8)	19 (13.5)	0.93
Other	39 (9.8)	8 (5.7)	0.14

*32 cases had two reasons for the revision **8 cases had two reasons for the revision

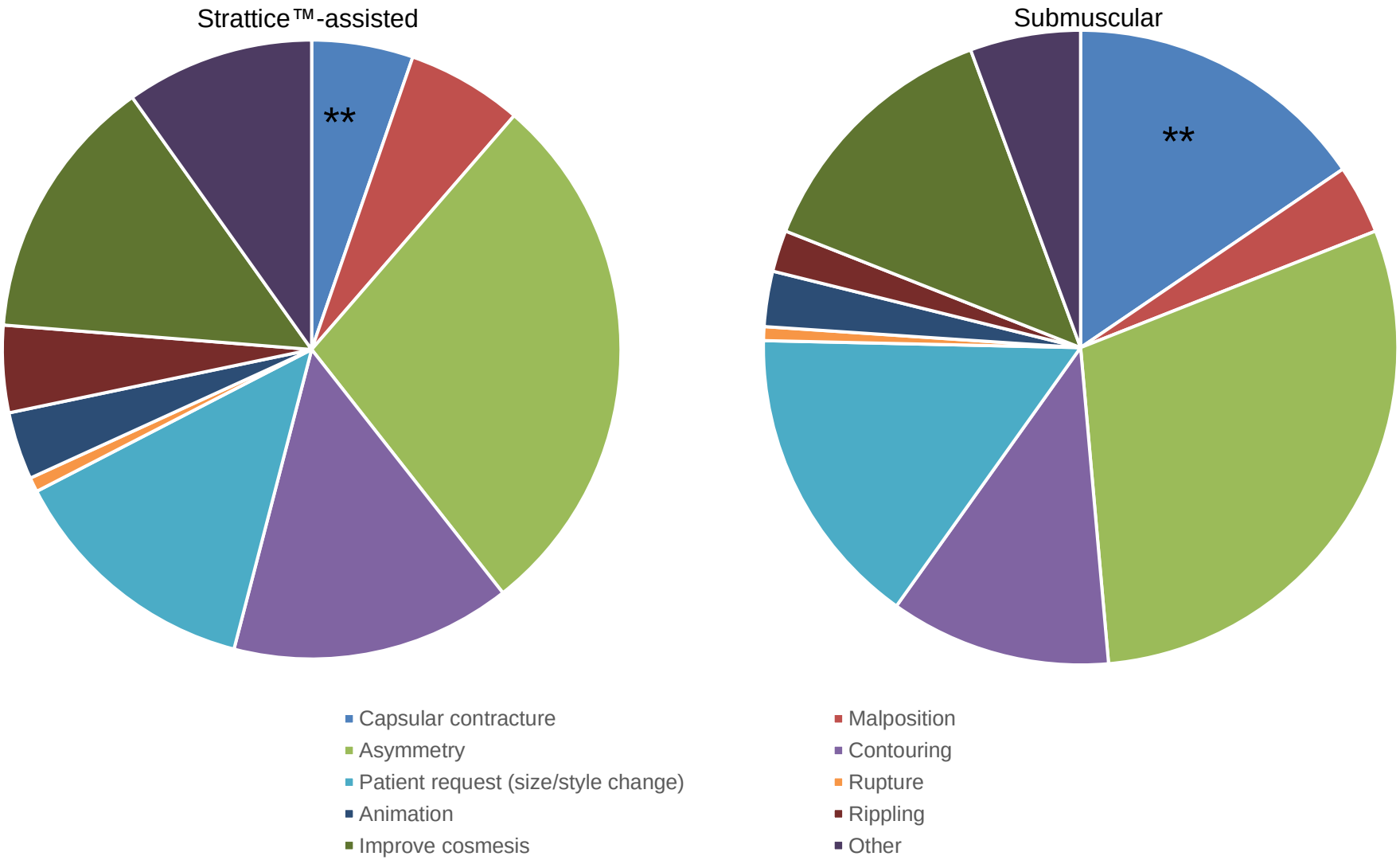


Figure 24 Reasons for revision surgery comparing Strattice™-assisted and submuscular reconstruction
** p<0.01

Time to 1st revision for capsular contracture

Less Strattice™-assisted reconstructions (n=20, 4.1%) had surgery for capsular contracture compared to the submuscular reconstructions (n=21, 10.9%), Log rank test, p=0.01, (Figure 25). There was no difference in the mean time to first revision surgery for capsular contracture of 29 months in Strattice™-assisted group and 37 months in the submuscular (p=0.29), however numbers are small.

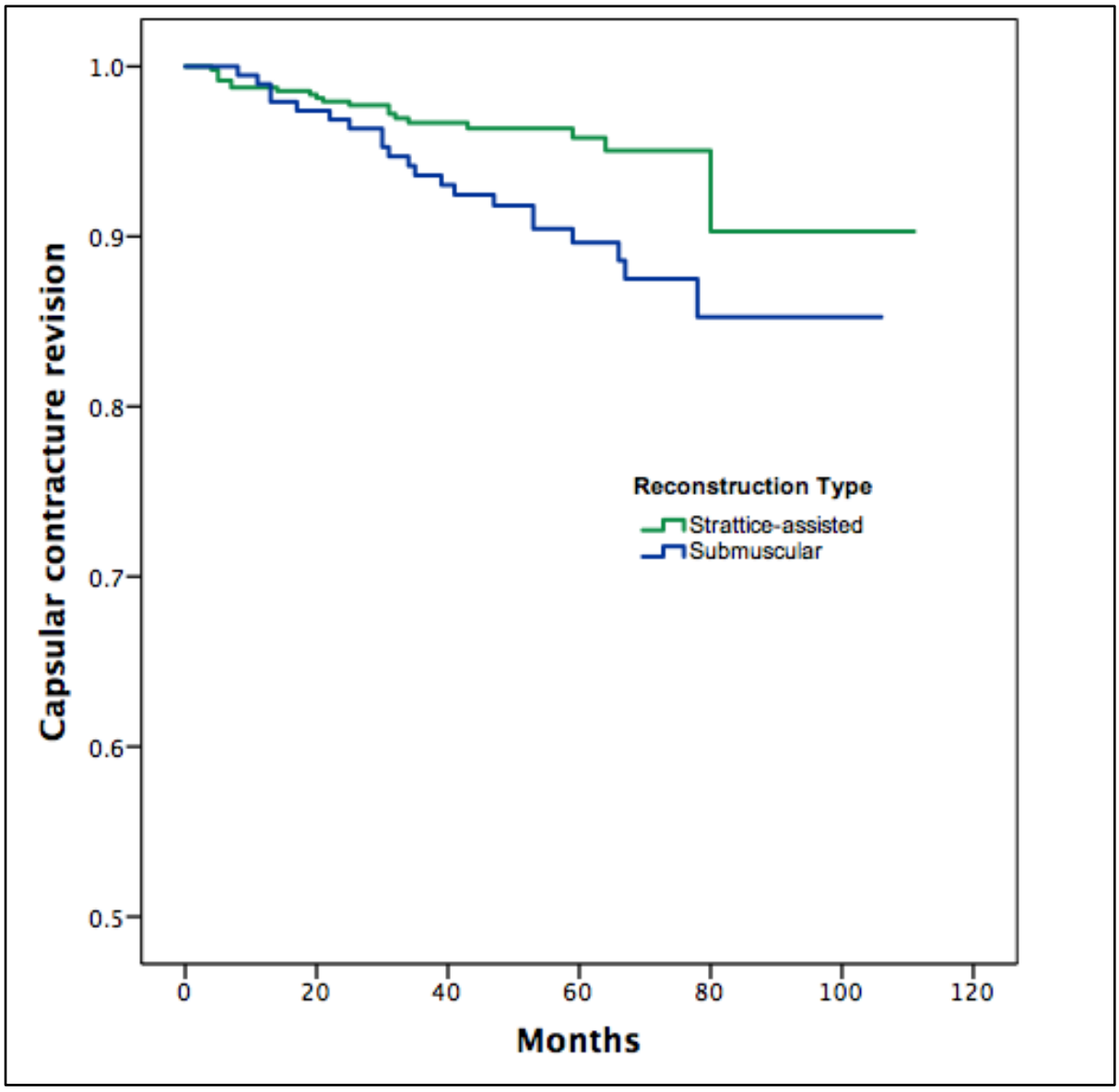


Figure 25 Kaplan Meier curve showing time to first revision for capsular contracture comparing Strattice™-assisted and submuscular reconstruction

Revision rates per centre

There was significant variation between the three centres in the number of Strattice™-assisted reconstructions that underwent revision surgery with centre 1 performing significantly less revisions than centre two and three (p<0.001). Centre two performed significantly more revisions in their Strattice™-assisted reconstructions than submuscular (p=0.049) (Figure 26).

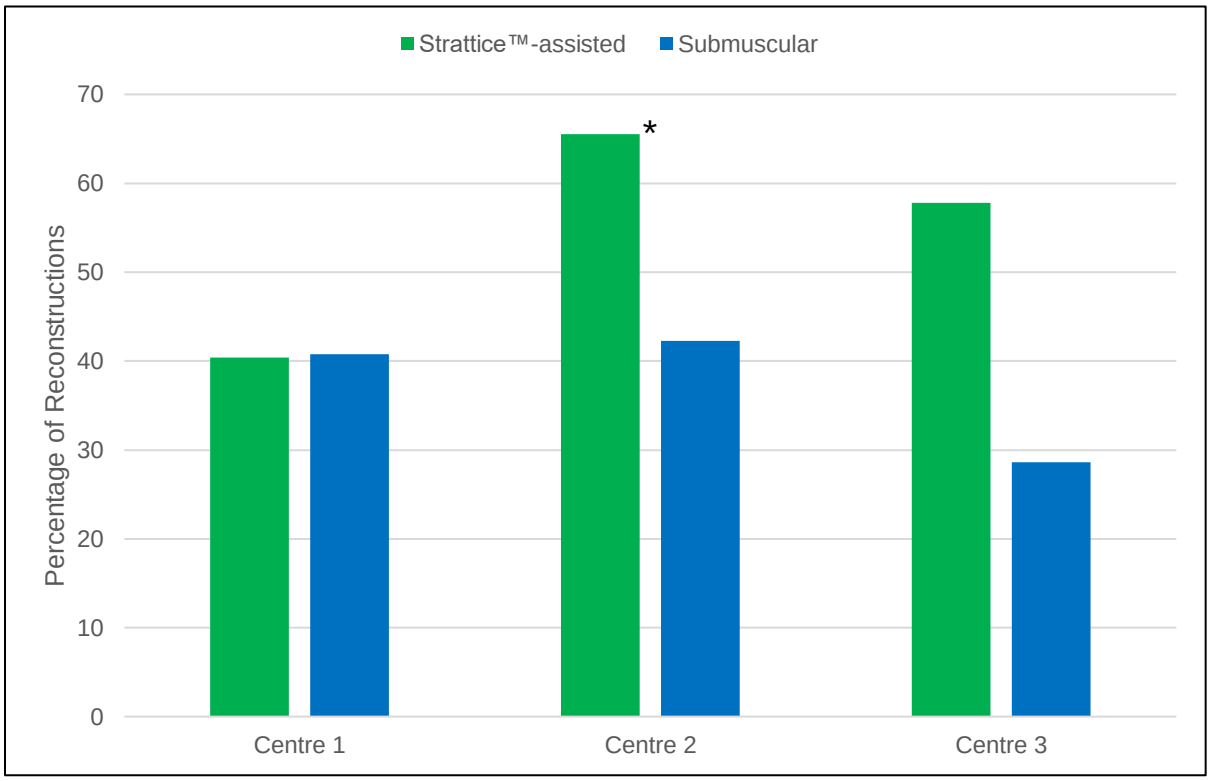


Figure 26 Revision rates comparing Strattice™-assisted and submuscular reconstructions per centre
*p<0.05 **p<0.001

3.1.8 Outcomes in direct to implant versus a two-stage procedure

Of the Strattice™-assisted reconstructions 383 (69.2%) were direct to implant, 96 (17.9%) were expander implants and 74 (13.4%) were two-staged procedures. Of the submuscular reconstructions 19 (7.9%) were direct to implant, 20 (8.3%) were expander implants and 203 (83.9%) were two-stage procedures.

There were no differences in post-operative complications between the direct to implant Strattice™-assisted and two-stage submuscular reconstructions (Table 25). Unplanned explantation rate as a complication of the primary surgery was 7.8% in the Strattice™-assisted direct to implant reconstructions compared to 5.9% in the two-stage submuscular reconstructions (p=0.39) (Figure 27).

Table 25 Post-operative complications comparing Strattice™-assisted direct to implant and two-stage submuscular reconstructions

	Direct to implant Strattice-assisted (%) n=383	**Two-stage submuscular (%) n=203**	**p value**
Haematoma	10 (2.6)	3 (1.5)	0.56
Infection			
Treated with oral antibiotics	37 (9.7)	21 (10.3)	0.79
Treated with IV antibiotics	10 (2.6)	2 (1.0)	0.23
Required surgical intervention	17 (4.4)	5 (2.5)	0.23
Delayed wound healing			
Treated conservatively	24 (6.3)	16 (7.9)	0.46
Required surgical intervention	40 (10.4)	6 (3.0)	0.32

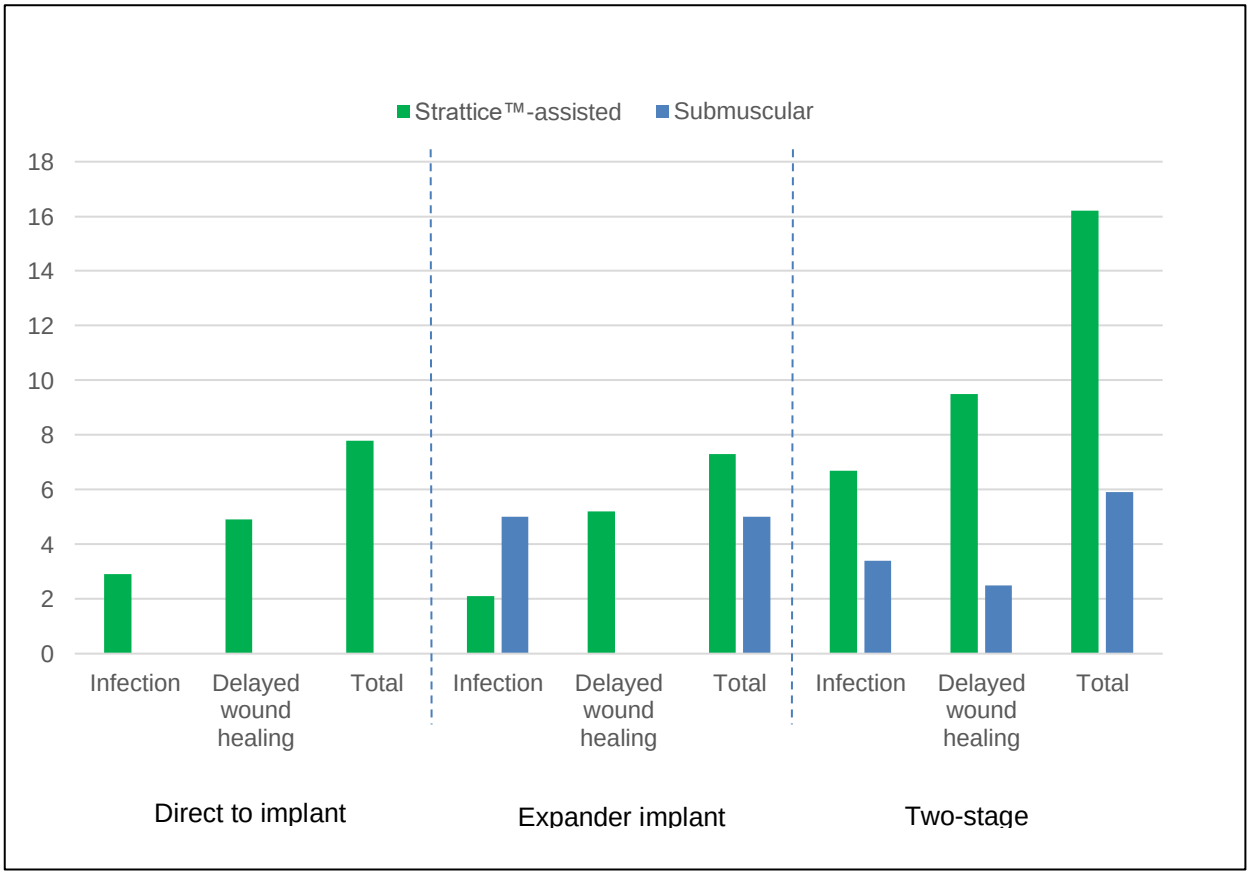


Figure 27 Reasons for implant loss in one and two-stage procedures comparing Strattice™-assisted and submuscular technique

3.1.9 Differences in outcome between therapeutic and risk reduction surgery in Strattice™-assisted breast reconstruction

There were 301 therapeutic Strattice™-assisted reconstructions performed and 252 for risk reduction. Median age was 51 years in the therapeutic group and 52 years in the risk reduction group. Except patients in the therapeutic group undergoing neo-adjuvant chemotherapy there was no other differences in pre-operative risk factors. Significantly more were treated with oral antibiotics for suspected infection in those whom had had the mastectomy and reconstruction for therapeutic reasons. Although more in the therapeutic group had a seroma the number requiring aspiration did not differ between the two groups (Table 26).

In the therapeutic group 207 had axillary surgery at the time of the reconstruction of whom 69 (33.3%) were treated for delayed wound healing or suspected infection, 94 had no axillary surgery or axillary surgery prior to their mastectomy and reconstruction and 21 (22.3%) were treated for delayed wound healing or suspected infection (p=0.05). A completion mastectomy was performed in 82 cases, 22 (26.8%) were treated for delayed wound healing or suspected infection compared to 68 (31.1%) in those that had not had a previous wide local excision.

In the risk reduction group, 12 had a completion mastectomy (initial WLE for cancer with clear margins but proceeded to mastectomy for risk reduction) of whom 4 (33.3%) were treated for delayed wound healing or suspected infection compared to 74 (30.8%) in those that had not.

Table 26 Post-operative complications comparing Strattice™-assisted reconstructions performed for therapeutic or risk reduction

	Therapeutic (%) n=301	**Risk reduction (%) n=252**	**p value**
Haematoma	7 (2.3)	5 (2)	1
Infection			
Treated with oral antibiotics	46 (15.3)	20 (7.9)	0.008
Treated with IV antibiotics	8 (2.7)	8 (3.2)	0.8
Required surgical intervention	15 (5)	15 (6)	0.7
Delayed wound healing			
Treated conservatively	13 (4.3)	18 (7.1)	0.2
Required surgical intervention	26 (8.6)	33 (13.1)	0.1
Seroma			
Present	84 (27.9)	45 (17.9)	0.006
Aspirated	34 (11.3)	22 (8.7)	0.4
>1 aspiration	13 (4.3)	10 (4)	1
Unplanned explantation			
Post-operative complications	26 (8.6)	21 (8.3)	1
Other	18 (6)	4 (1.6)	0.008

3.1.10 Differences in outcome between skin sparing and nipple sparing mastectomy in Strattice™-assisted breast reconstruction

There were 424 skin sparing (nipple sacrificing) mastectomies (260 (61.3%) therapeutic, 164 (38.7%) risk reduction) and 119 nipple sparing mastectomies (32 (26.9%) therapeutic, 87 (73.1%) risk reduction), performed in the Strattice™-assisted group. Post-operative complications were equivalent between skin sparing and nipple sparing mastectomies except for more nipple sparing mastectomies were treated for delayed wound healing, specifically those managed conservatively (Table 27).

Table 27 Post-operative complications comparing skin sparing and nipple sparing mastectomies in Strattice™-assisted reconstructions

	Skin sparing (%) n=424	**Nipple sparing (%) n=119**	**p value**
Haematoma	14 (3.3)	1 (0.8)	0.21
Infection			0.45
Treated with oral antibiotics	51 (12.0)	12 (10.1)	0.56
Treated with IV antibiotics	10 (2.4)	6 (5.0)	0.13
Required surgical intervention	27 (6.4)	3 (2.5)	0.12
Delayed wound healing			0.01
Treated conservatively	16 (3.8)	15 (12.6)	0.002
Required surgical intervention	45 (10.6)	14 (11.8)	0.72
Seroma			
Present	100 (23.6)	28 (23.5)	0.99
Aspirated	39 (9.2)	17 (14.3)	0.11
>1 aspiration	18 (4.2)	5 (4.2)	1
Unplanned explantation			
Post-operative complications	36 (8.5)	10 (8.4)	1
Other	19 (4.5)	2 (1.7)	0.28

3.1.11 Change in practice over time

In the first three years after the introduction of Strattice™ to the three units there was an increase in numbers performed with a subsequent decrease in the number of submuscular reconstructions performed (Figure 28). In the first year Strattice-assisted reconstructions were performed the number of unplanned explantations secondary to post-operative complications was significantly higher than in the submuscular group, 21.4% vs. 4.3%, p=0.05 (Figure 29), there was no difference in subsequent years.

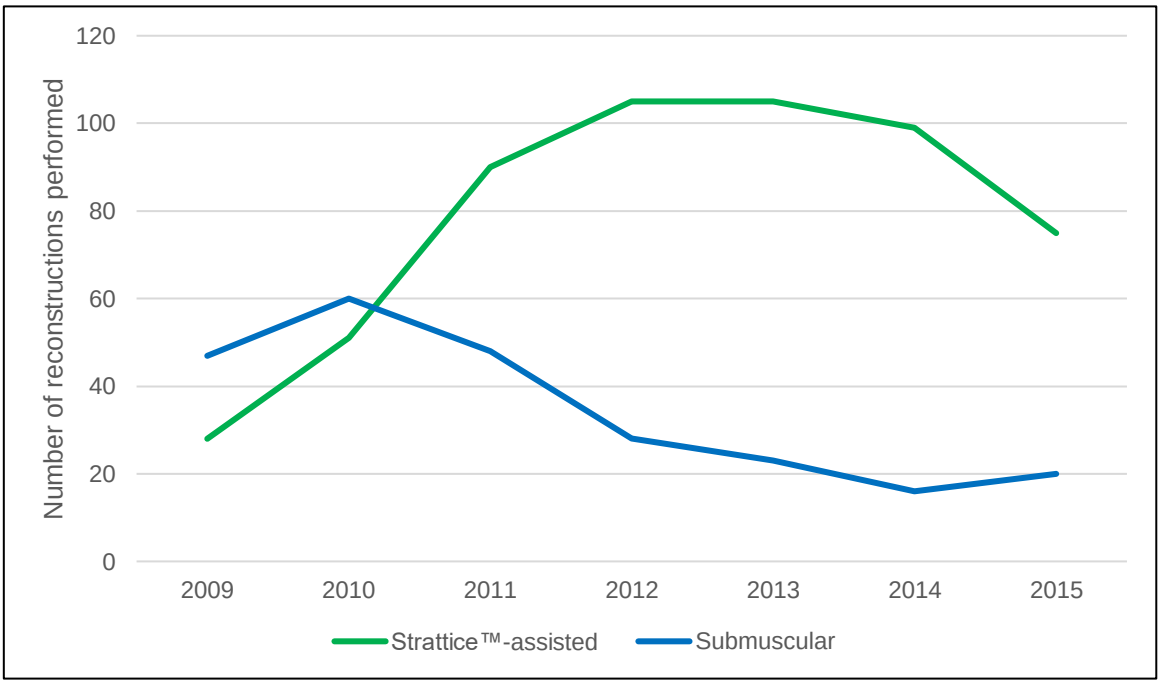


Figure 28 Trends over time comparing Strattice™-assisted and submuscular reconstructions

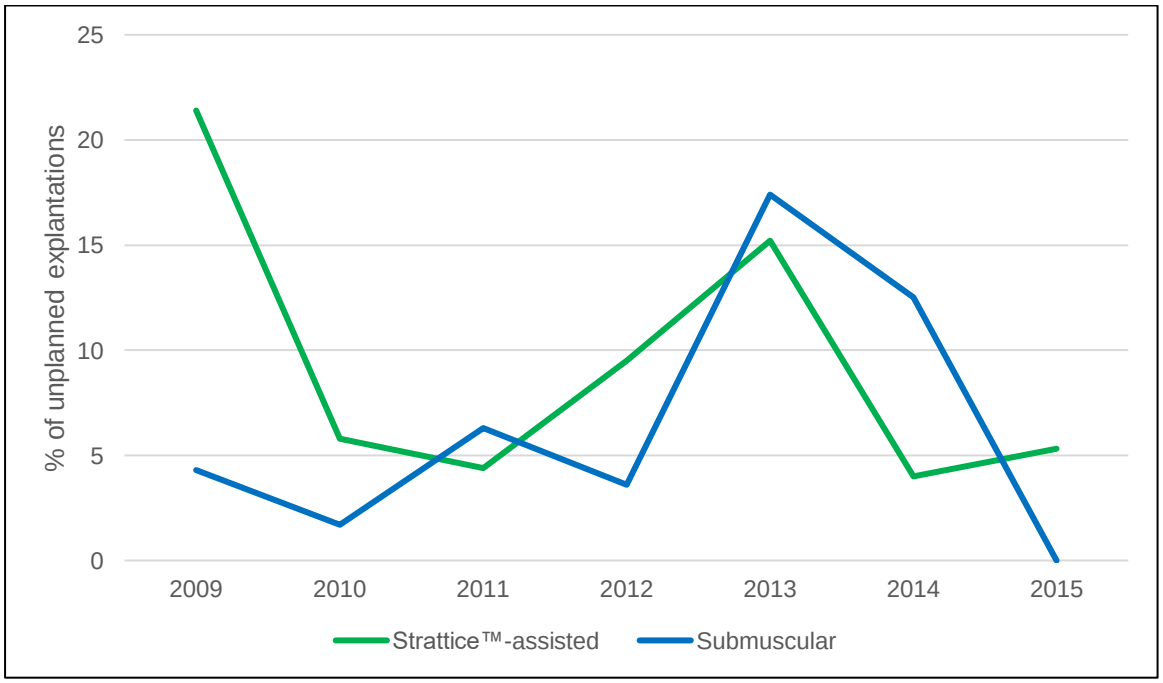


Figure 29 Trends over time of unplanned explantation secondary to post-operative complications comparing Strattice™-assisted and submuscular reconstructions

When Strattice™ was first introduced more expander implants were used, however as time progressed the number of direct to implant reconstructions increased (Figure 30). The size of implants used varied from year to year with no specific trend over time. On average over 30% were >400cc and no increase in implant loss rate was observed in this cohort (Figure 31). Throughout the whole study period the mean ratio of mastectomy weight to implant volume was 1:1.13 in the Strattice™-assisted group and 1:1.21 in the submuscular group (p=0.1) (Table 28).

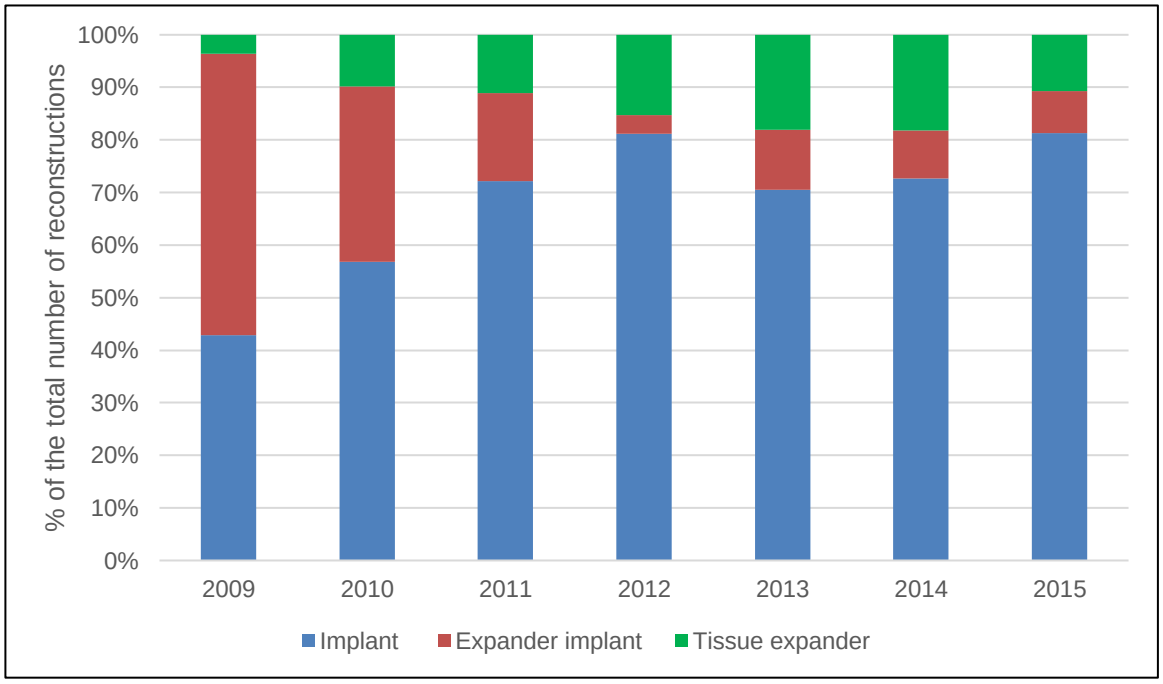


Figure 30 Trends over time of type of prosthesis used in Strattice™-assisted reconstructions

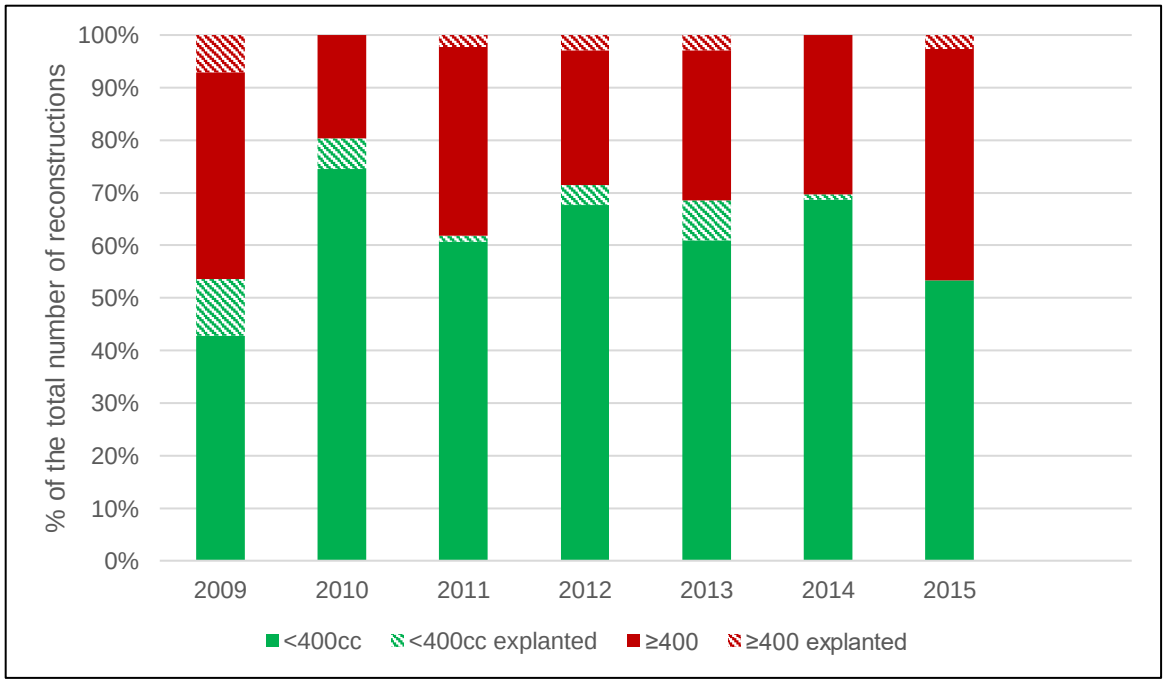


Figure 31 Trends over time of size of definitive implant used in Strattice™-assisted reconstructions and unplanned explantation of implant secondary to wound dehiscence or skin necrosis

Table 28 Trends over time of mean ratio of mastectomy weight to implant volume in Strattice™-assisted and submuscular reconstructions

Year	Strattice™-assisted	Submuscular	p value
2009	1:0.93	1:1.05	0.3
2010	1:1.33	1:1.32	0.9
2011	1:1.12	1:1.10	0.8
2012	1:1.10	1:1.05	0.6
2013	1:1.02	1:1.33	0.7
2014	1:1.23	1:1.69	0.1
2015	1:1.10	1:1.23	0.4

3.1.12 Cost effectiveness using Strattice™ for direct to implant reconstructions

Price analysis was performed with data from one trust as part of a sub study in collaboration with Rong Khaw (CT2 Plastic Surgery). Each procedure was assigned a healthcare resource group (HRG) code to determine a price, valid within the NHS. 130 patients with a minimum of five years follow-up underwent 171 immediate implant based breast reconstruction. 109 direct to implant Strattice™-assisted (77 patients) and 54 two stage submuscular (47 patients) reconstructions were included.

Total mean price of the index reconstructive procedure is £3,634 Strattice™-assisted and £4,230 submuscular. In the Strattice™-assisted group 44 (57%) patients had further planned procedures; 15 contralateral surgeries, 52 nipple reconstructions and 22 removals of Becker™ port at a mean price of £1,026 per reconstruction. In the submuscular group 22 (47%) patients had further planned procedures; 18 contralateral surgeries and 15 nipple reconstructions at a mean price of £1,016.

Unplanned procedures for either post-operative complications or revision of the reconstruction were performed on 57 (52%) reconstructions in the Strattice™-assisted group and 28 (52%) in the submuscular group at a mean price of £1,846 and £1,920 respectively.

Mean five-year total price was £6,506 for the Strattice™-assisted reconstructions versus £7,166 for the submuscular (p=0.2).

3.2 Clinical cohort study - assessing rates of capsular contracture, cosmetic and patient reported outcomes in Strattice™-assisted and submuscular reconstructions

3.2.1 Summary of methods

A cohort study comparing rates of capsular contracture, cosmetic and patient reported outcomes, using clinical examination and tonometry, photographs and Breast Q, between Strattice™-assisted or submuscular reconstructions.

3.2.2 Recruitment to the BROWSE Study

Within the three sites 117 patients who had undergone 169 Strattice™-assisted reconstruction and 49 patients who had undergone 65 submuscular were recruited to the study. Centre one recruited 67 Strattice™-assisted and 49 submuscular, Centre two 11 Strattice™-assisted and one submuscular and Centre 3 37 Strattice™-assisted (Figure 32).

3.2.3 Demographics of the study group

The median age of the Strattice™-assisted group was 54 years (range 29 – 75 years) compared to 56 years (range 41 – 79 years) in the submuscular group. As in the retrospective cohort, there were younger women and fewer smokers in the Strattice™-assisted group but no other difference in demographics or pre-operative risk factors (Table 29). The median follow-up was five years two months (range two years five months to nine years five months) in the Strattice™-assisted group and six years four months (range three years two months to nine years three months) in the submuscular group (p=0.0001).

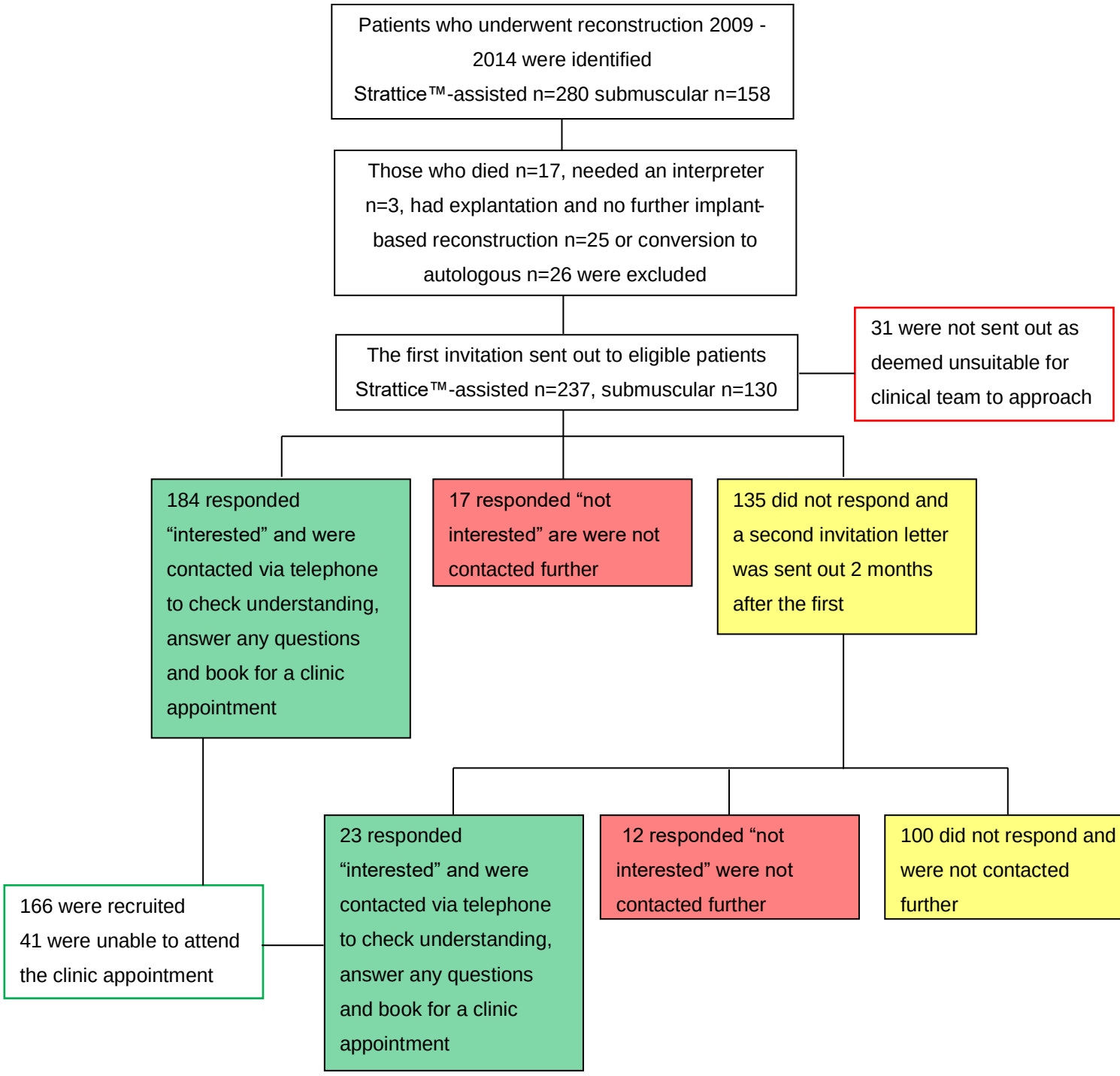


Figure 32 Recruitment to the BROWSE Study

Table 29 Patient demographics and peri-operative risk factors

	Strattice™-assisted n (%) n=117	Submuscular n (%) n=49	p value
Age (years)			
<40	15 (12.8)	0	0.006
40-60	59 (50.4)	31 (63.3)	0.13
>61	43 (36.8)	18 (36.7)	0.68
BMI (kg/m2)			
≤17.9	2 (1.7)	2 (4.1)	0.58
18.0-24.9	63 (53.8)	29 (59.2)	0.53
25.0-29.9	43 (36.8)	13 (26.5)	0.2
≥30	9 (7.7)	5 (10.2)	0.56
Smoking Status			
Smoker	8 (6.8)	8 (16.3)	0.06
Non-smoker	98 (83.8)	40 (81.6)	0.74
Ex-smoker	11 (9.4)	1 (2.0)	0.11
Diabetes	3 (2.6)	1 (2.0)	1
Previous chest wall radiotherapy	6 (5.1)	3 (6.1)	0.72

3.2.4 Assessment of capsular contracture

Baker Grade

Of the 169 Strattice™-assisted reconstructions examined (117 patients, 52 bilateral cases) 17 (10.1%) were graded Baker 3 or 4 compared to 6 (9.2%) of the 65 (49 patients, 16 bilateral cases) submuscular reconstructions (p=0.85). In the Strattice™-assisted group 6 (3.6%) of those graded with a Baker 1 or 2 capsule had previously undergone surgery to correct capsular contracture compared to 8 (13.6%) in the submuscular group (p=0.01). This gives an estimated rate of capsular contracture in the Strattice™-assisted group of 13.6% and 21.5% in the submuscular (p=0.14) (Figure 33).

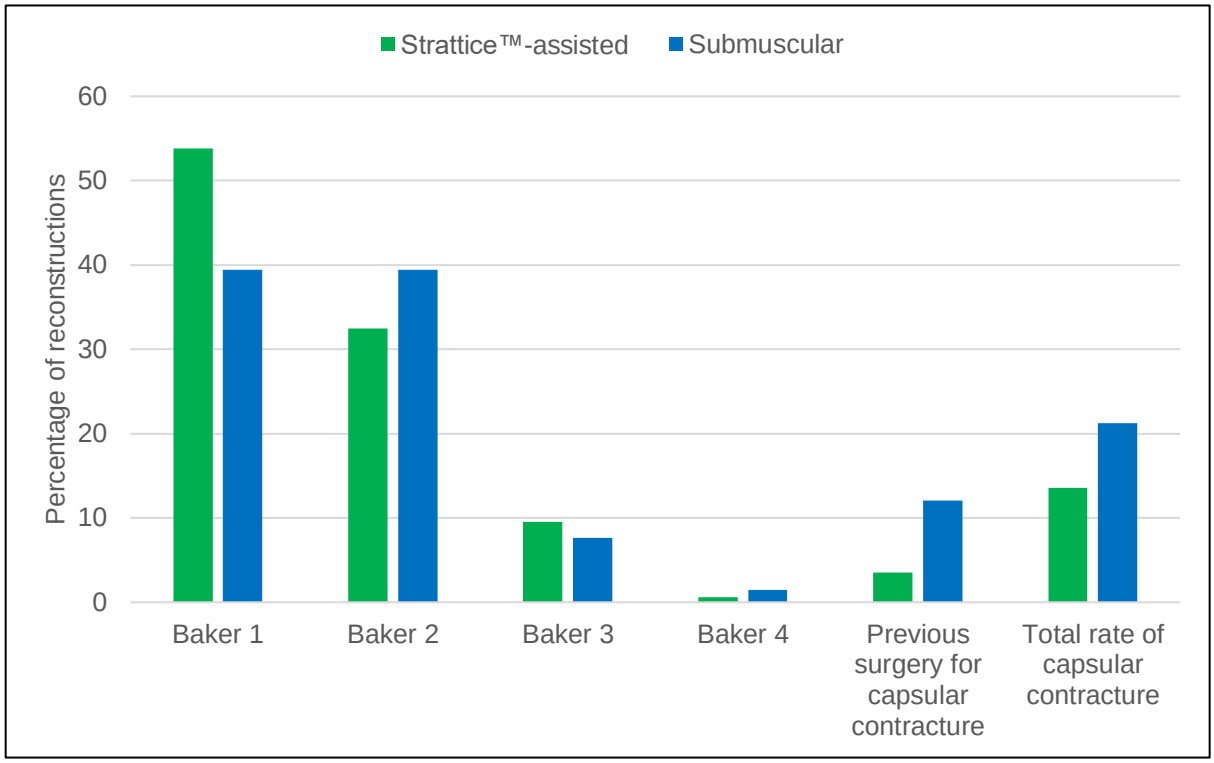


Figure 33 Percentage of reconstructions with each Baker grade on examination or had previously undergone revision surgery for capsular contracture comparing Strattice™-assisted and submuscular reconstructions

Patient reporting of Baker Grade

When the patients were asked to grade their own breasts using the same scale, in the Strattice™-assisted group 48 were upgraded by the patient and 29 were downgraded. In the submuscular group 22 were upgraded by the patient and 11 downgraded (Figure 34).

In both the Strattice™-assisted and submuscular group the agreement between clinician and patient of Baker Grade was considered ‘fair’ using both Kappa statistic (0.234 and 0.219 respectively) and weighted Kappa (0.352 and 0.334) (Figure 35).

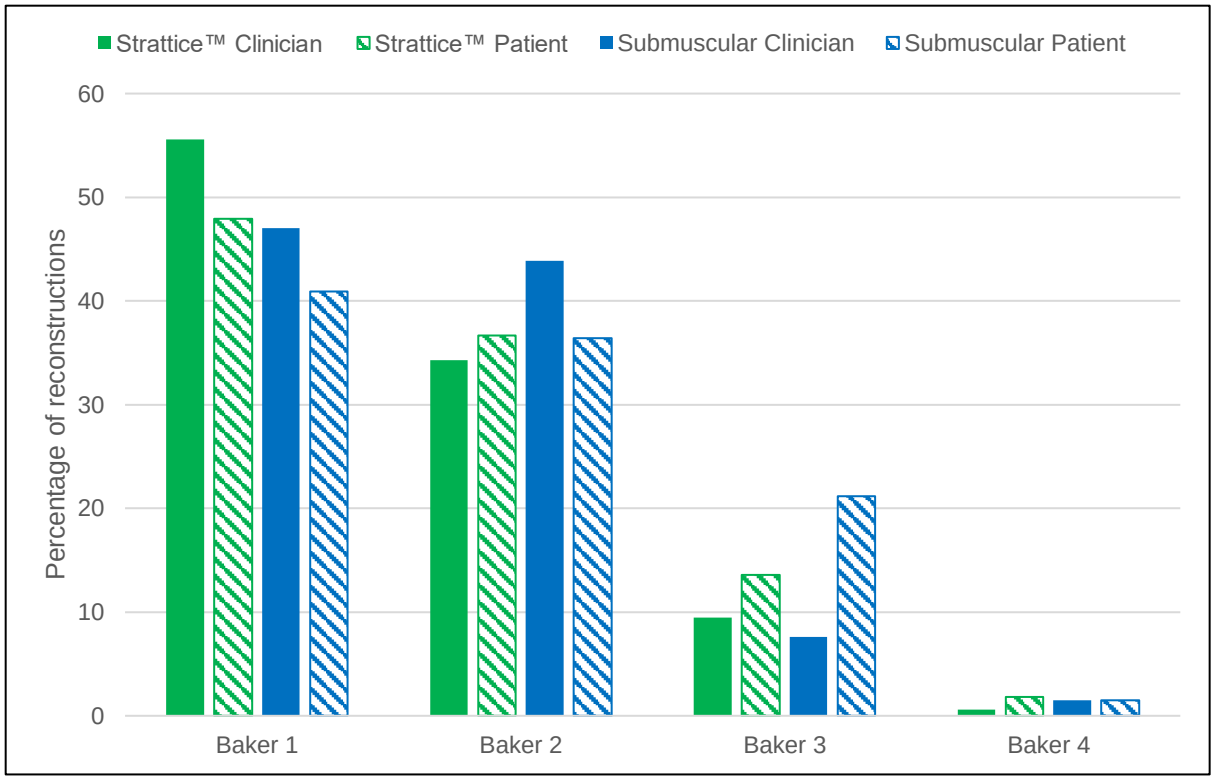


Figure 34 Percentage of reconstructions with each Baker grade on examination by clinician and on assessment by patient comparing Strattice™-assisted and submuscular reconstructions

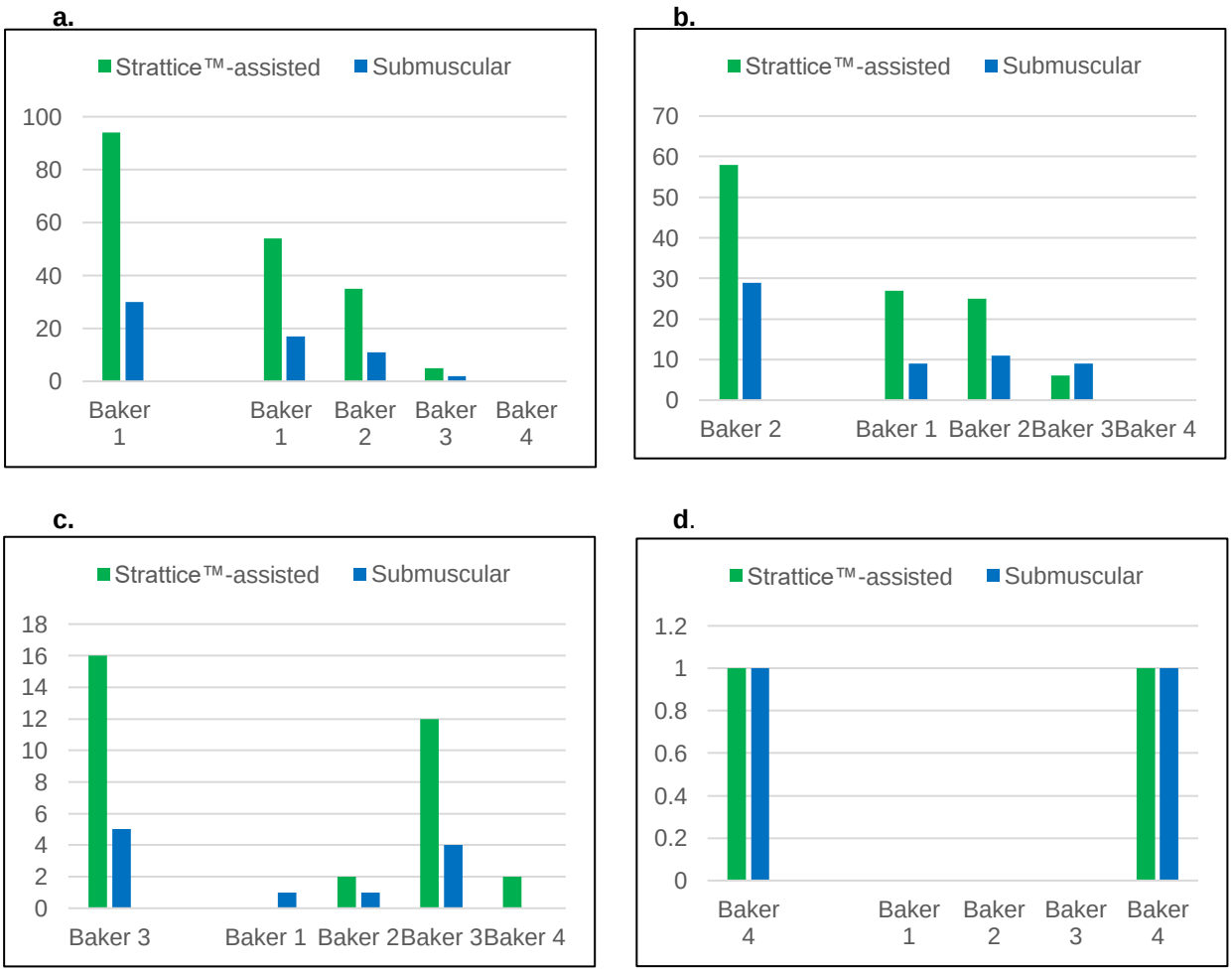


Figure 35 Comparison between the number of clinician assessed Baker grade reconstructions with patient assessed Baker grade reconstruction when given a description of each Baker grade in Strattice™-assisted and submuscular reconstructions **a.** Clinician graded Baker 1, **b.** Clinician grade Baker 2. **c.** Clinician graded Baker 3, **d**. Clinician graded Baker 4

Tonometry

Tonometry had a weak negative correlation with Baker grade ($r=-0.28$, $p<0.001$). Baker 1/2 capsules had a higher (softer) mean reading of 5.4 compared to 4.8 in Baker 3/4 capsules however there was no significant difference between the readings of the two groups (Figure 36).

There was no evidence of a difference in mean tonometry reading between reconstruction type ($p=0.36$).

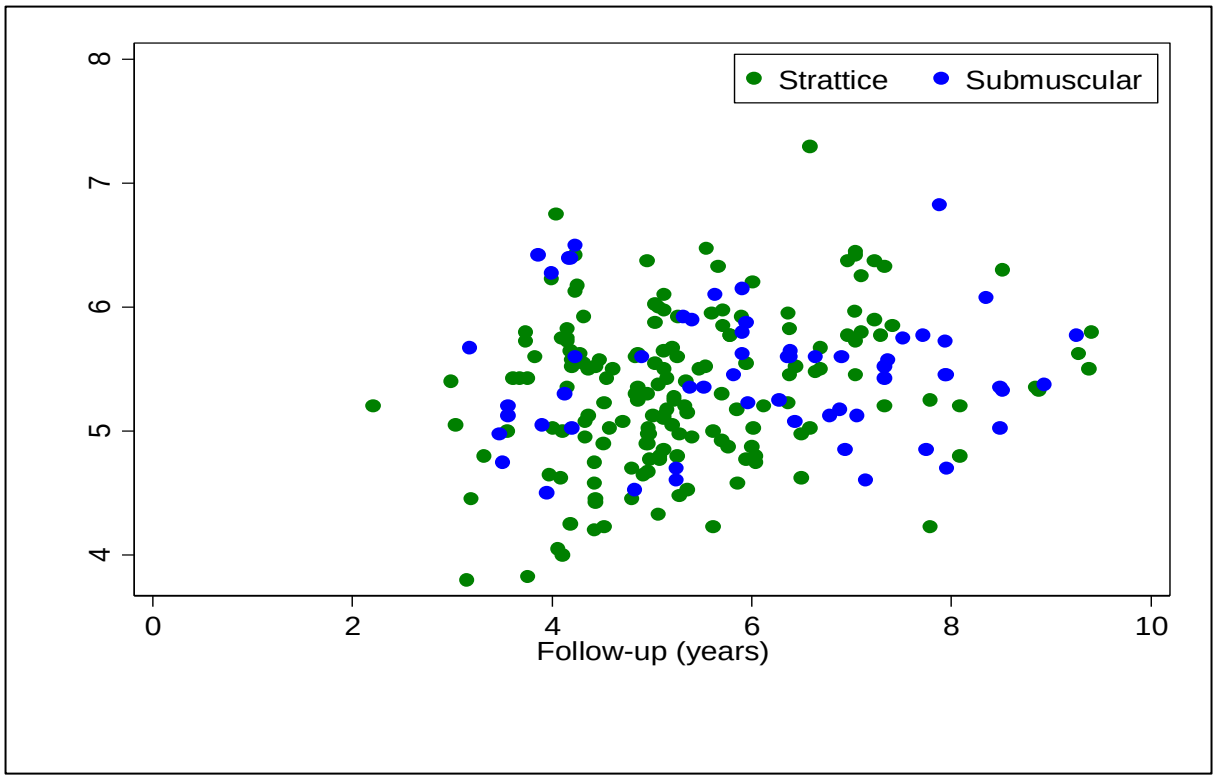


Figure 36 Mean tonometry readings over time comparing Strattice™-assisted and submuscular reconstructions

3.2.5 Risk factors for capsular contracture

In the Strattice™-assisted group 67 (57.3%) patients experienced a complication (according to review of the medical records) compared to 30 (61.2%) in the submuscular group (p=0.73) (Table 30).

Table 30 Post-operative complications comparing the Strattice™-assisted and submuscular reconstructions in the recruited patients

	Strattice™-assisted n (%) Breasts=169	**Submuscular n (%) Breasts=65**	**p value**
Haematoma	3 (1.8)	1 (1.5)	1
Infection			
Treated with oral antibiotics	26 (15.4)	3 (4.6)	0.03
Treated with IV antibiotics	6 (3.6)	1 (1.5)	0.68
Required surgical intervention	8 (4.7)	0	0.11
Delayed wound healing			
Treated conservatively	6 (3.6)	8 (12.3)	0.03
Required surgical intervention	14 (8.3)	1 (1.5)	0.07
Seroma			
Present	44 (26.0)	26 (40.0)	0.06
Aspirated	17 (10.1)	15 (23.1)	0.02

In the Strattice™-assisted group 23 (13.6%) reconstructions had capsular contracture (defined as Baker III/IV on clinical examination or previous surgery for capsular contracture), 11 (48%) experienced a complication. Eight were treated for suspected infection, three had wound dehiscence, one had evacuation of haematoma, three had a seroma (one required aspiration) and two had implant loss with revision of reconstruction. The rate of capsular contracture if there had been a complication was 14.1% compared to 13.2% if there had not (p=1).

In the submuscular group 14 (21.2%) reconstructions had capsular contracture, 11 (79%) experienced a complication. Three had a wound dehiscence and ten had a seroma (seven required aspiration). The rate of capsular contracture if there had been a complication was 33.3% compared to 9.1% if there had not (p=0.03).

Previous or adjuvant radiotherapy was administered in 14 (8.4%) of the Strattice™-assisted reconstructions. Seven (50%) developed capsular contracture. In the submuscular group six (9.2%) had had radiotherapy, one (16.7%) developed capsular contracture (p=0.32).

3.2.6 Aesthetic assessment

Photographs were taken of 153 Strattice™-assisted reconstructions and 59 submuscular. The photographs were assessed by a blinded panel consisting of one consultant oncoplastic breast surgeon, one breast care nurse and one lay person. There was a significantly higher general satisfaction score in the Strattice™-assisted group from all three panel members (Figure 37).

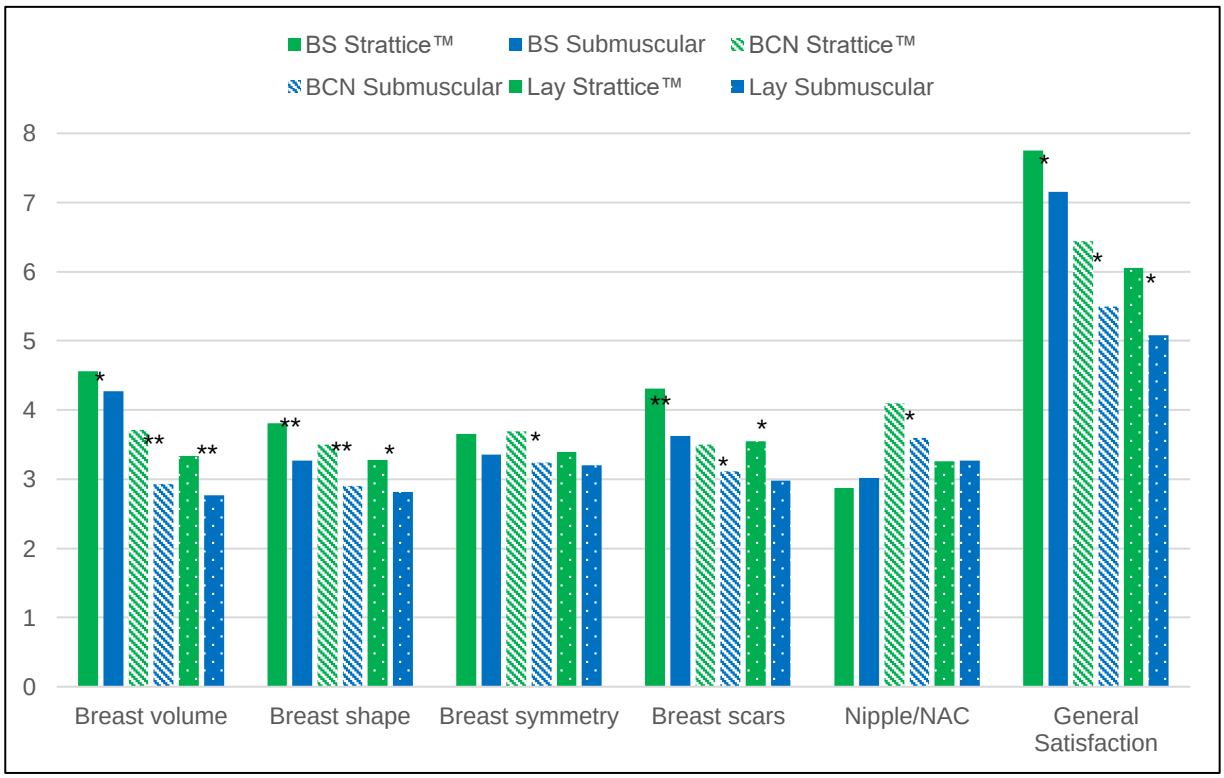


Figure 37 Mean aesthetic scores comparing Strattice™-assisted and submuscular reconstructions from breast surgeon (BS), breast care nurse (BCN) and lay person (lay) when using the 10 point Visser scale (62) (1-10 for general satisfaction 1-5 for other categories)
* <0.05 ** <0.01

Intra and inter rater reliability

Internal controls (repeated images) were placed within the presentation to assess intra-operator reliability. The breast surgeon had excellent reliability in scoring breast shape and nipple/NAC and the breast care nurse had good reliability in all aspects except nipple/NAC (Figure 38).

There was good inter-rater reliability between the breast surgeon, breast care nurse and lay person for scoring of breast symmetry and general satisfaction (ICC 0.87 and 0.79 respectively). For scoring of breast volume, breast shape, breast scars and nipple/NAC there was moderate reliability (ICC 0.66, 0.71, 0.74 and 0.68). The greatest reliability across all 6 categories was between the breast surgeon and the breast care nurse followed by breast care nurse and lay person then breast surgeon and lay person.

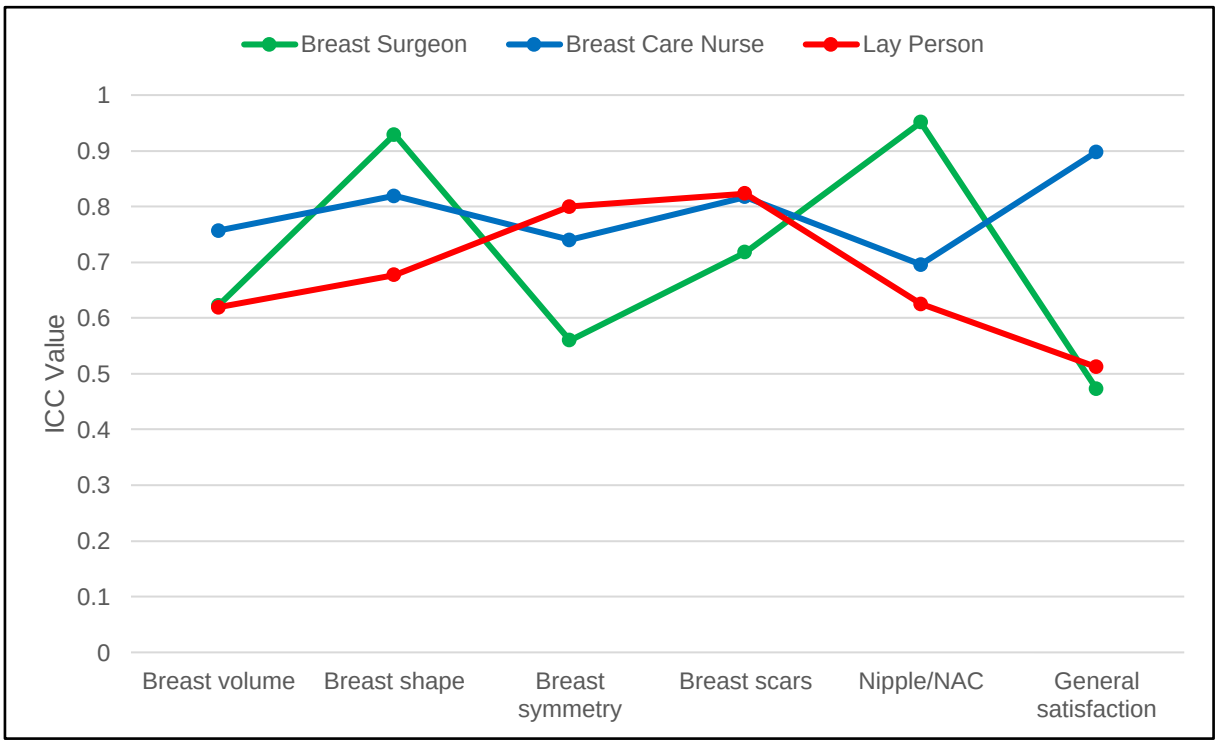


Figure 38 Intra-rater reliability using the intra class coefficient of breast surgeon, breast care nurse and lay person in the aesthetic scoring of Strattice™-assisted and submuscular implant based reconstructions
ICC Values <0.5 poor, 0.5-0.74 moderate, 0.75-0.9 good, >0.9 excellent reliability

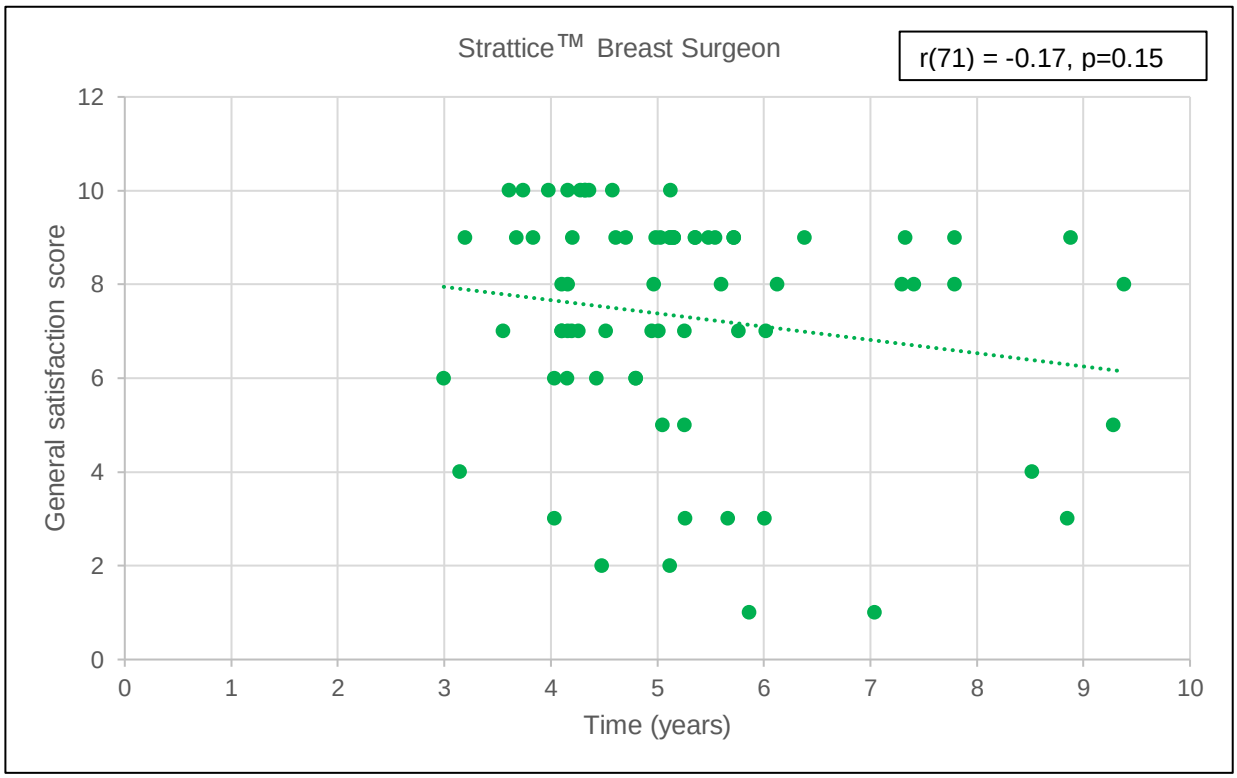
Comparison of cosmetic score with time

There was no significant correlation between general satisfaction score and time in either the Strattice™-assisted or submuscular reconstructions who had no revision surgery during the follow-up period (Figure 39).

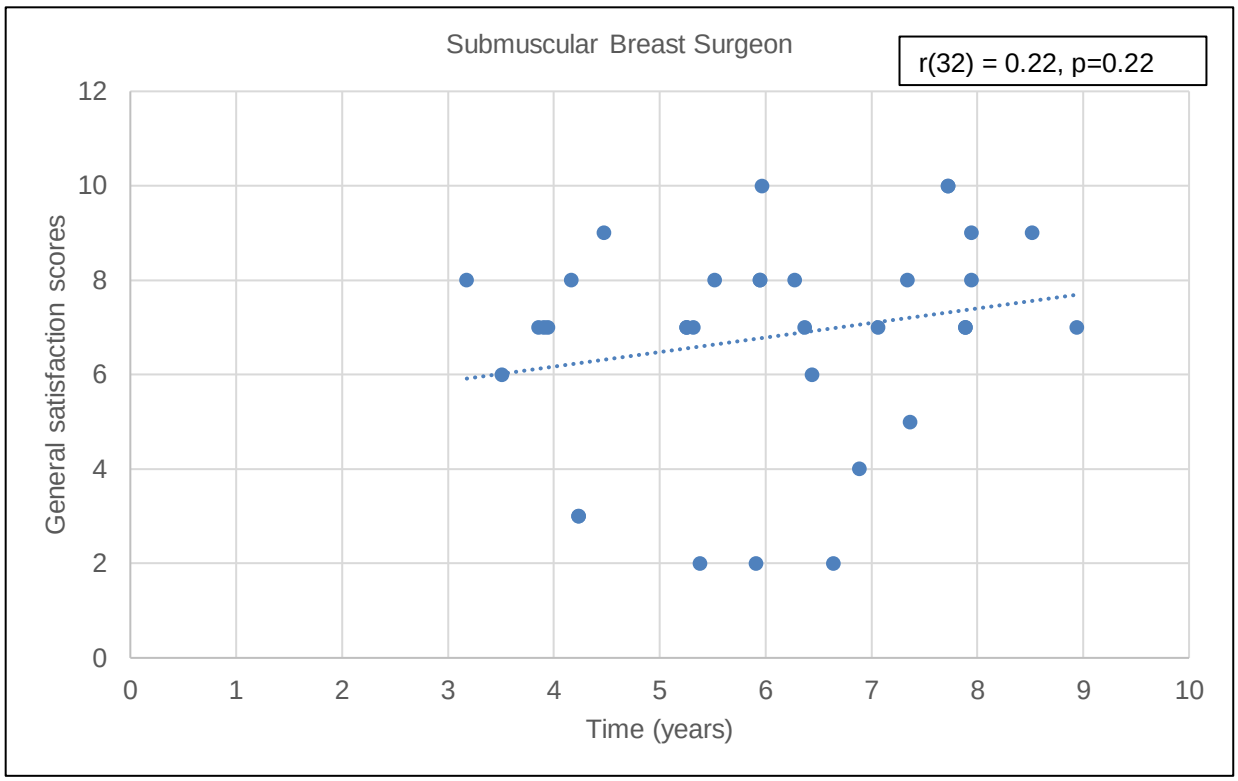
The mean general satisfaction score was 6.68 in those that developed a complication in the Strattice™-assisted group compared to 5.57 in the submuscular group (p=0.004).

The mean general satisfaction score was lower in Strattice™-assisted reconstructions that developed a complication than those that did not when scored by the breast care nurse and lay person and a mean of all three assessors, this was not significant. The mean general satisfaction score was lower in submuscular reconstructions that developed a complication than those that did not when scored by all three assessors, this was not significant.

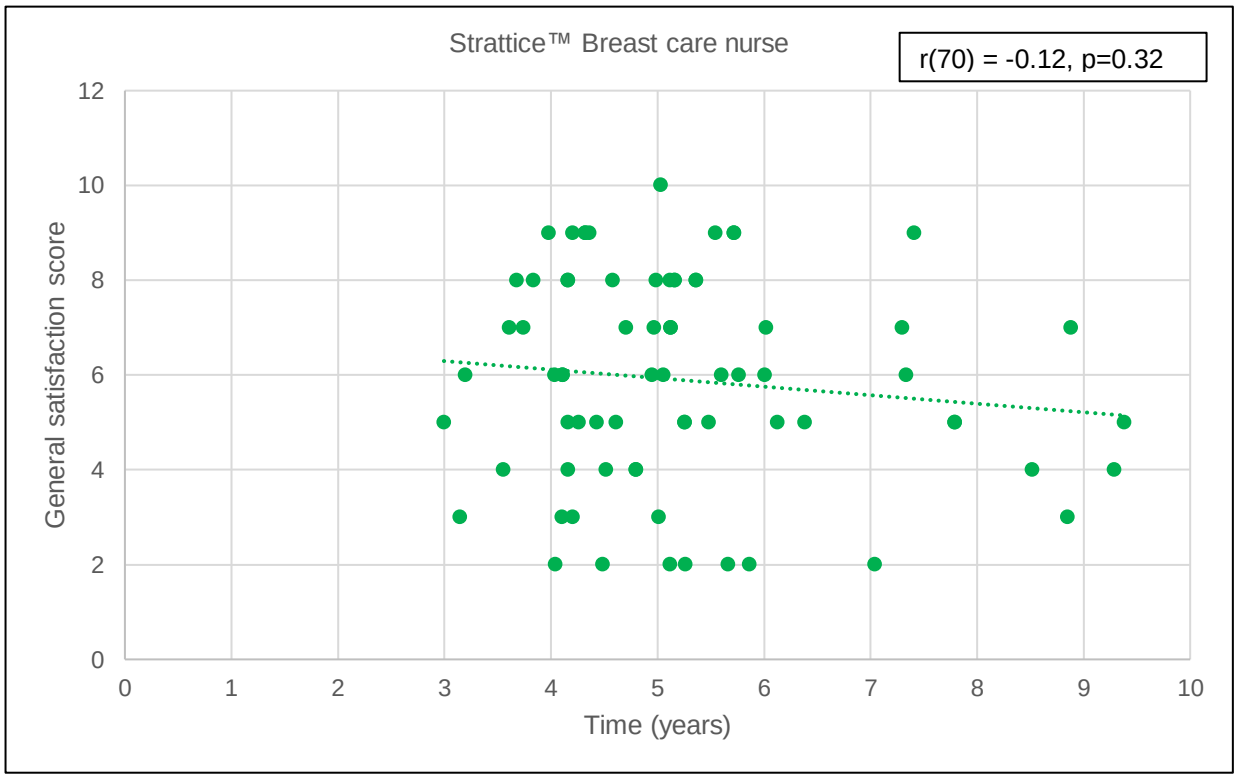
a.


Strattice™ Breast Surgeon
r(71) = -0.17, p=0.15
General satisfaction score
Time (years)
0
2
4
6
8
10
12
0
1
2
3
4
5
6
7
8
9
10

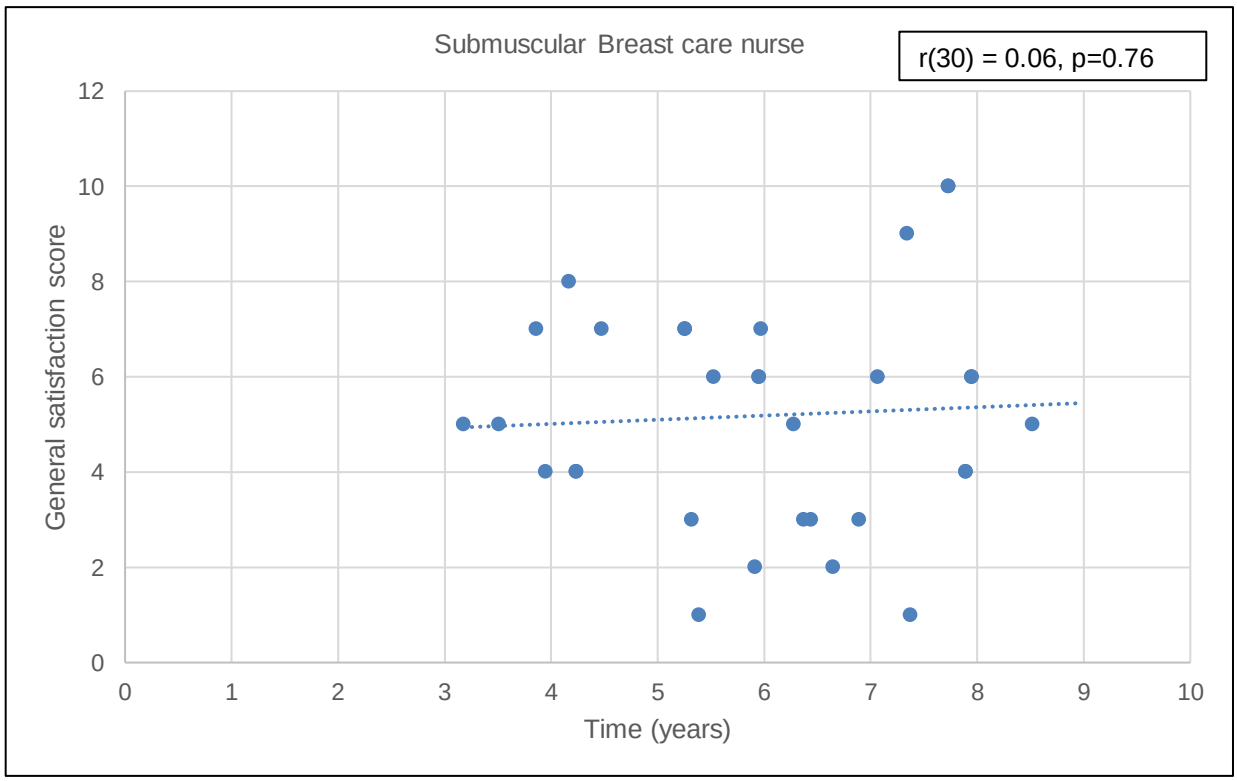
b.


Submuscular Breast Surgeon
r(32) = 0.22, p=0.22
General satisfaction scores
Time (years)
0
2
4
6
8
10
12
0
1
2
3
4
5
6
7
8
9
10

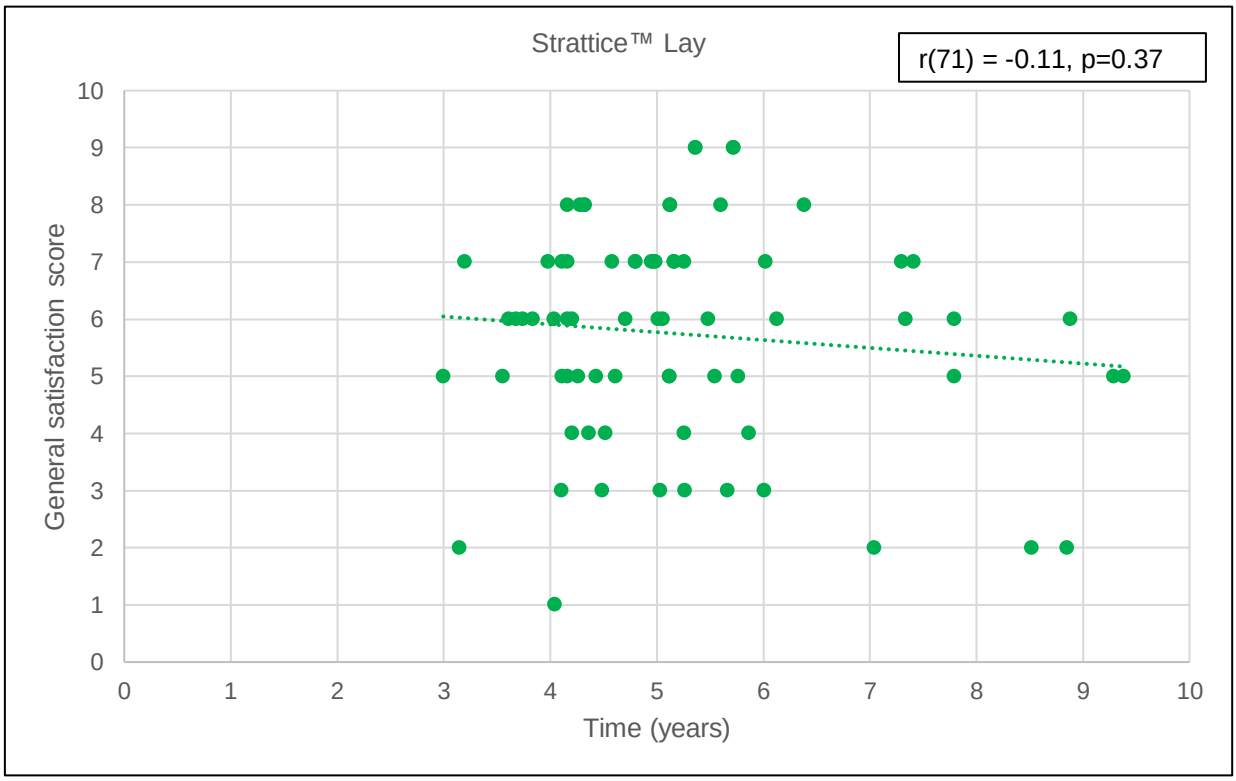
c.


Strattice™ Breast care nurse
r(70) = -0.12, p=0.32
General satisfaction score
Time (years)
0
2
4
6
8
10
12
0
1
2
3
4
5
6
7
8
9
10

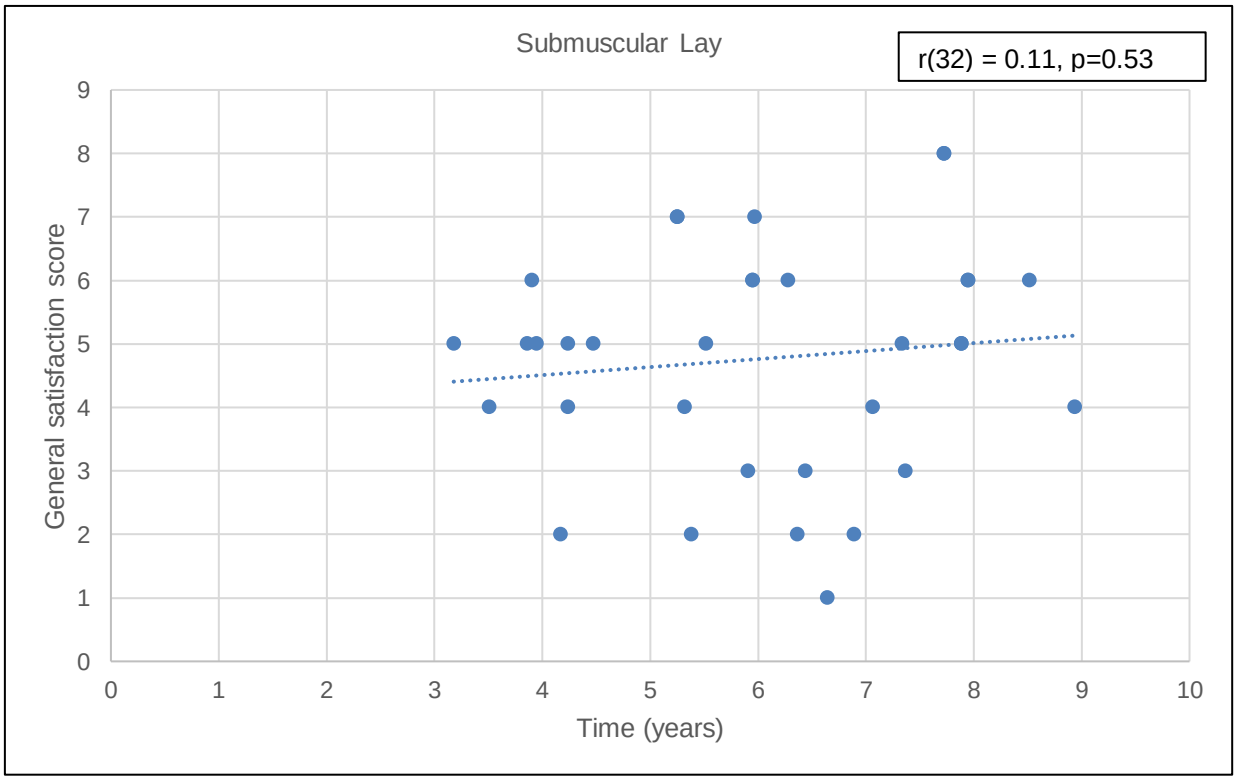
d.


Submuscular Breast care nurse
r(30) = 0.06, p=0.76
General satisfaction score
Time (years)
0
2
4
6
8
10
12
0
1
2
3
4
5
6
7
8
9
10

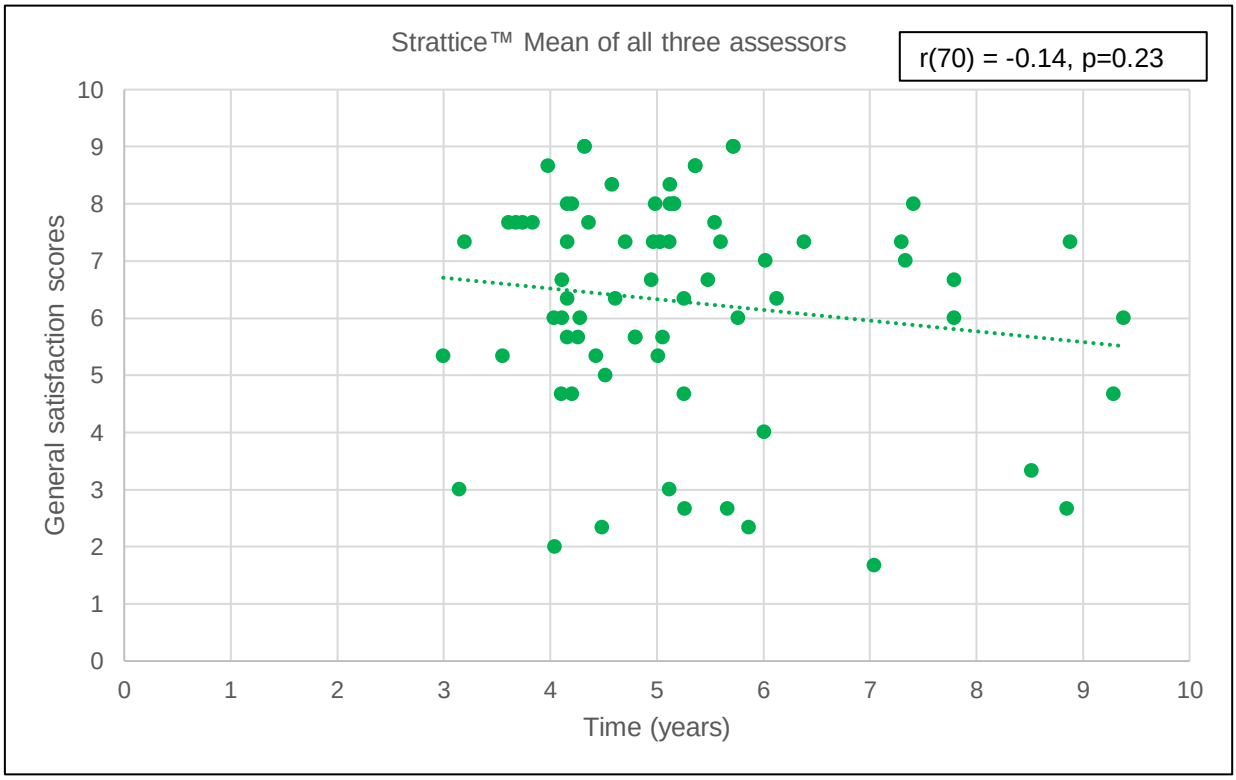
e.


Strattice™ Lay
r(71) = -0.11, p=0.37
General satisfaction score
Time (years)
0
1
2
3
4
5
6
7
8
9
10

f.


Submuscular Lay
r(32) = 0.11, p=0.53
General satisfaction score
Time (years)
0
1
2
3
4
5
6
7
8
9
10

g.



h.

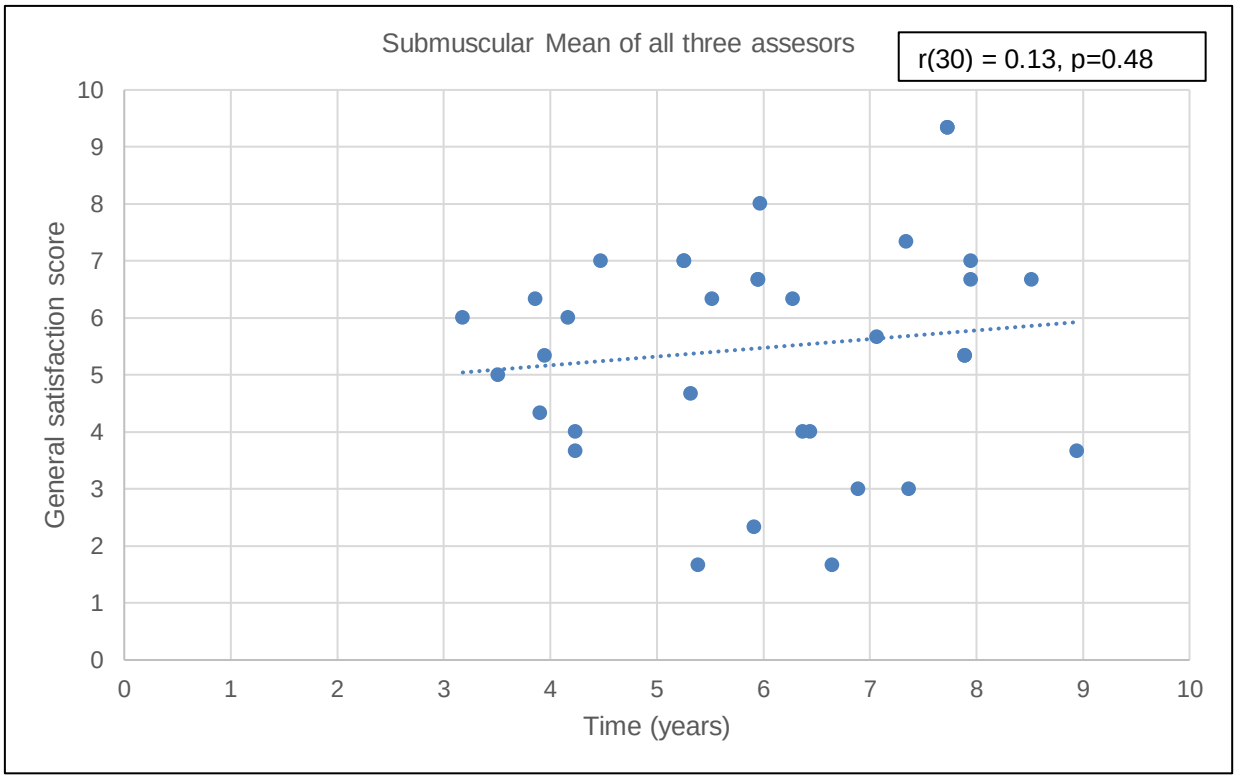


Figure 39 General satisfaction scores over time in Strattice™ and submuscular reconstructions who did not undergo any revision surgery
a. Strattice™ reconstructions and **b.** submuscular reconstructions scored by Breast Surgeon,
c. Strattice™ reconstructions and **d.** submuscular reconstructions scored by Breast care nurse
e. Strattice™ reconstructions and **f.** submuscular reconstructions scored by lay person
g. Strattice™ reconstructions and **h.** submuscular reconstructions mean score of all three assessors

Comparison of aesthetic scores per unit

Strattice™-assisted reconstructions performed at Centre two scored highest by all three independent blinded assessors (Figure 40)

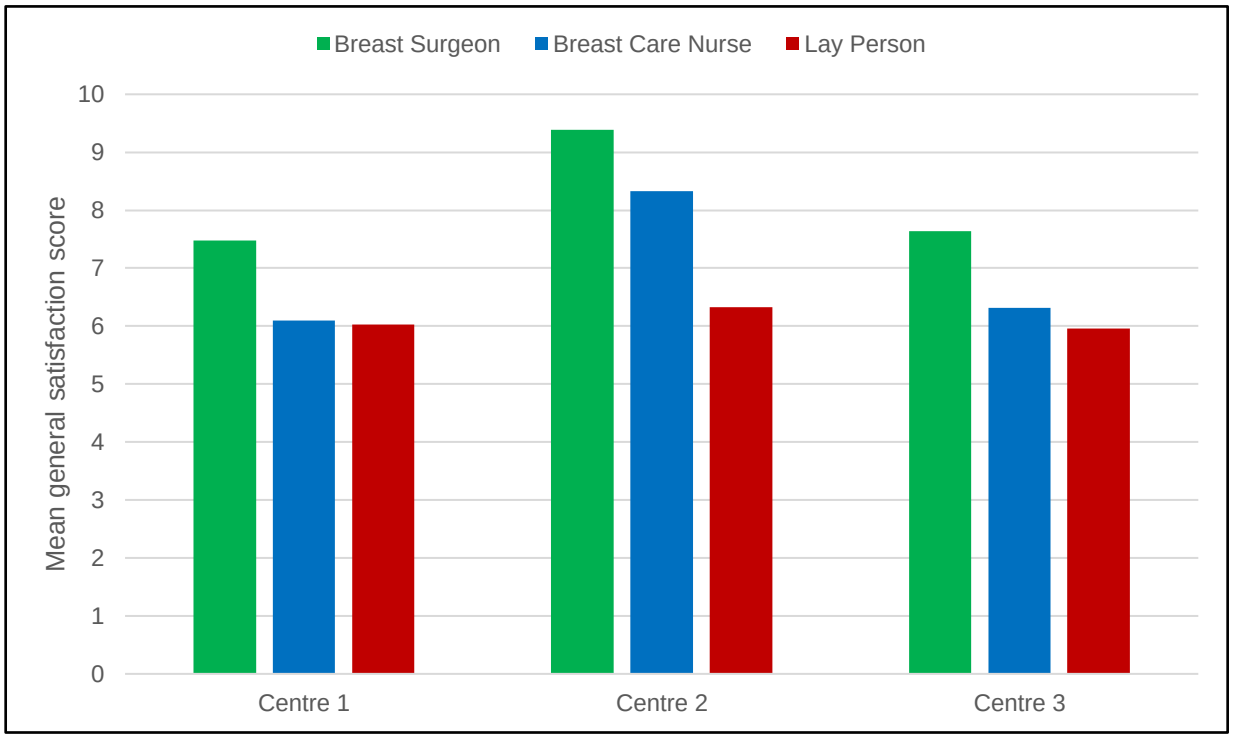


Figure 40 Comparison of the mean general satisfaction score of Strattice™-assisted reconstructions per centre

3.2.7 Quality of life using the BREAST-Q score

There was a 93% response rate, 106 responses were received from patients who underwent a Strattice™-assisted reconstruction and 47 from patients who underwent a submuscular reconstruction. There was no difference in mean domain score between the Strattice™-assisted and submuscular group (Figure 41).

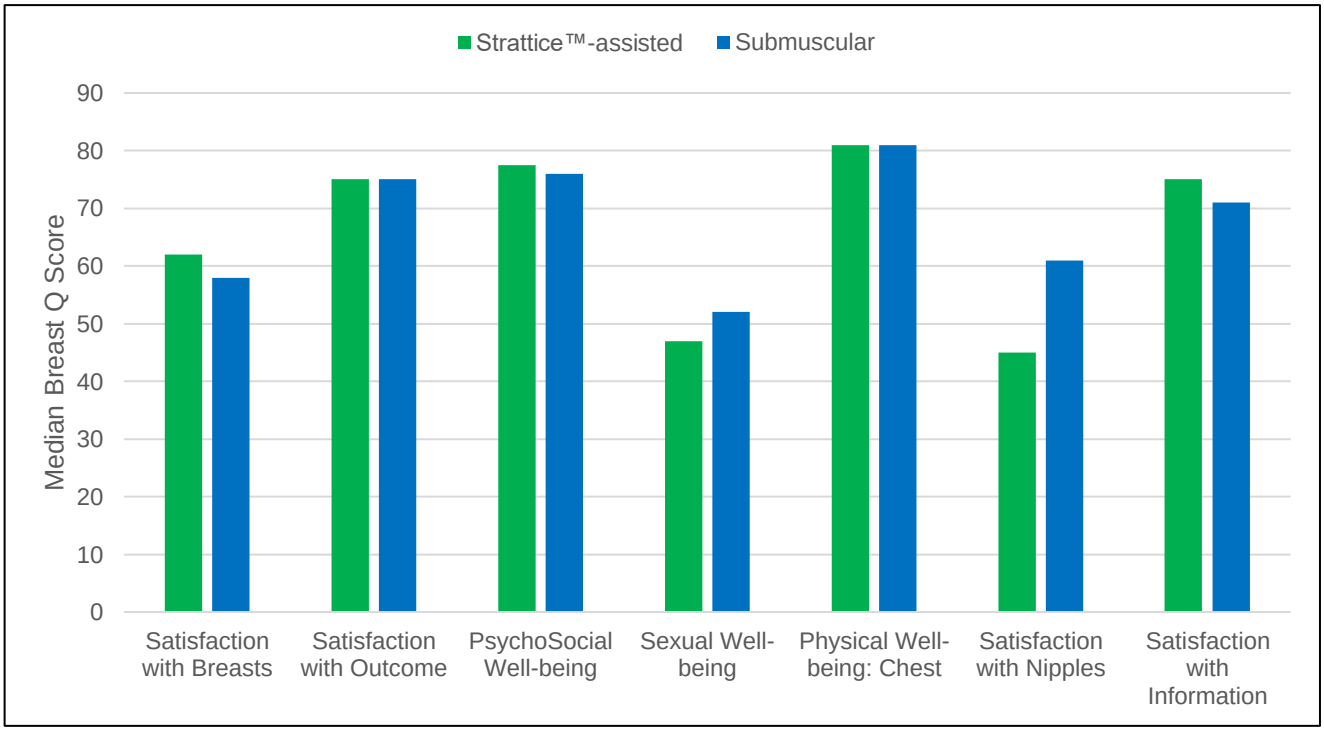


Figure 41 Median BREAST-Q scores comparing Strattice™-assisted and submuscular reconstructions
40 (35%) in the Strattice™-assisted group and 20 (41%) in the submuscular group had nipple reconstruction

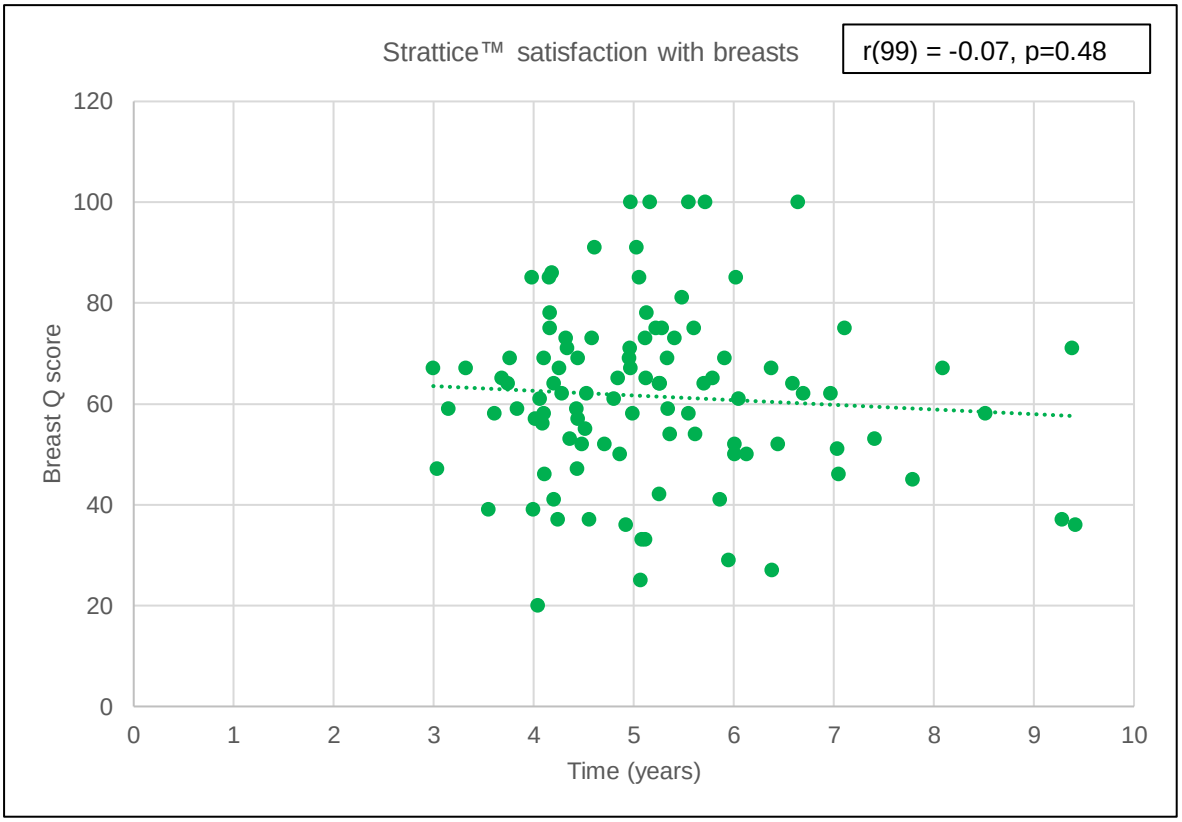
There was no significant difference between the BREAST-Q scores of those that had a complication in the Strattice™-assisted group compared to the submuscular group.

Within the Strattice™-assisted reconstructions there was no significant difference in any domain of the BREAST-Q scores when comparing patients that developed a complication to those who did not.
Within the submuscular reconstructions there was no significant difference in any domain of the BREAST-Q scores when comparing patients that developed a complication to those who did not.

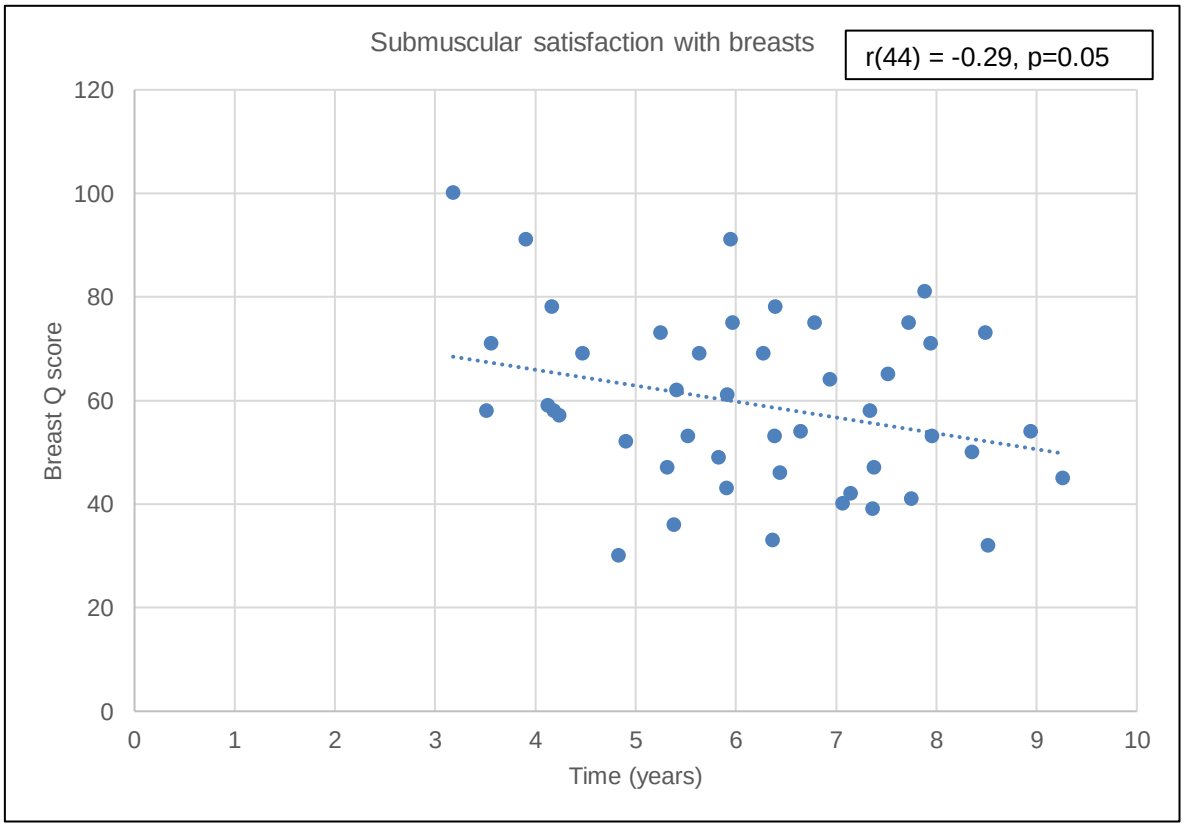
Comparison of quality of life with time

There was a decline in satisfaction with breasts and satisfaction with outcome over time in the submuscular group ($r(44) = -0.29$, $p=0.05$, $r(44) = -0.28$, $p=0.06$) but no correlation in the other domains in either the Strattice™-assisted or submuscular reconstructions (Figure 42).

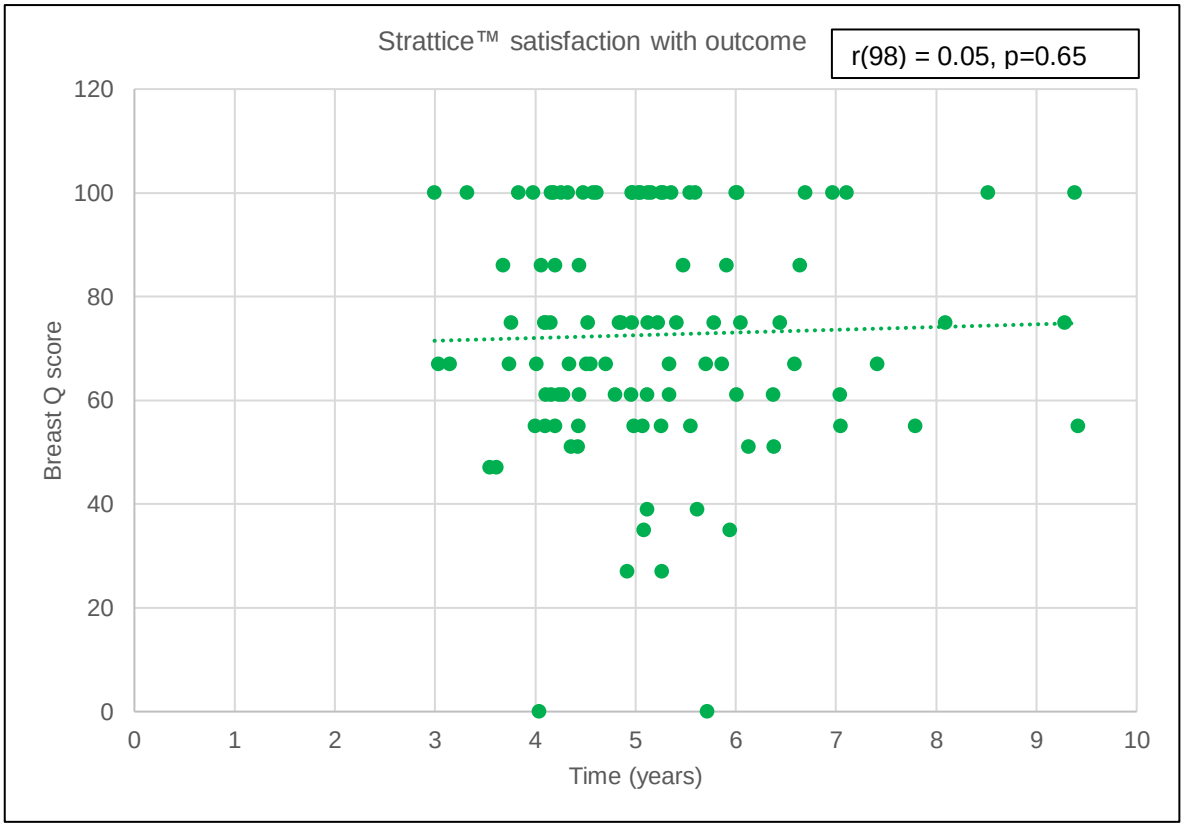
a.


Strattice™ satisfaction with breasts
r(99) = -0.07, p=0.48
Breast Q score
Time (years)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
10

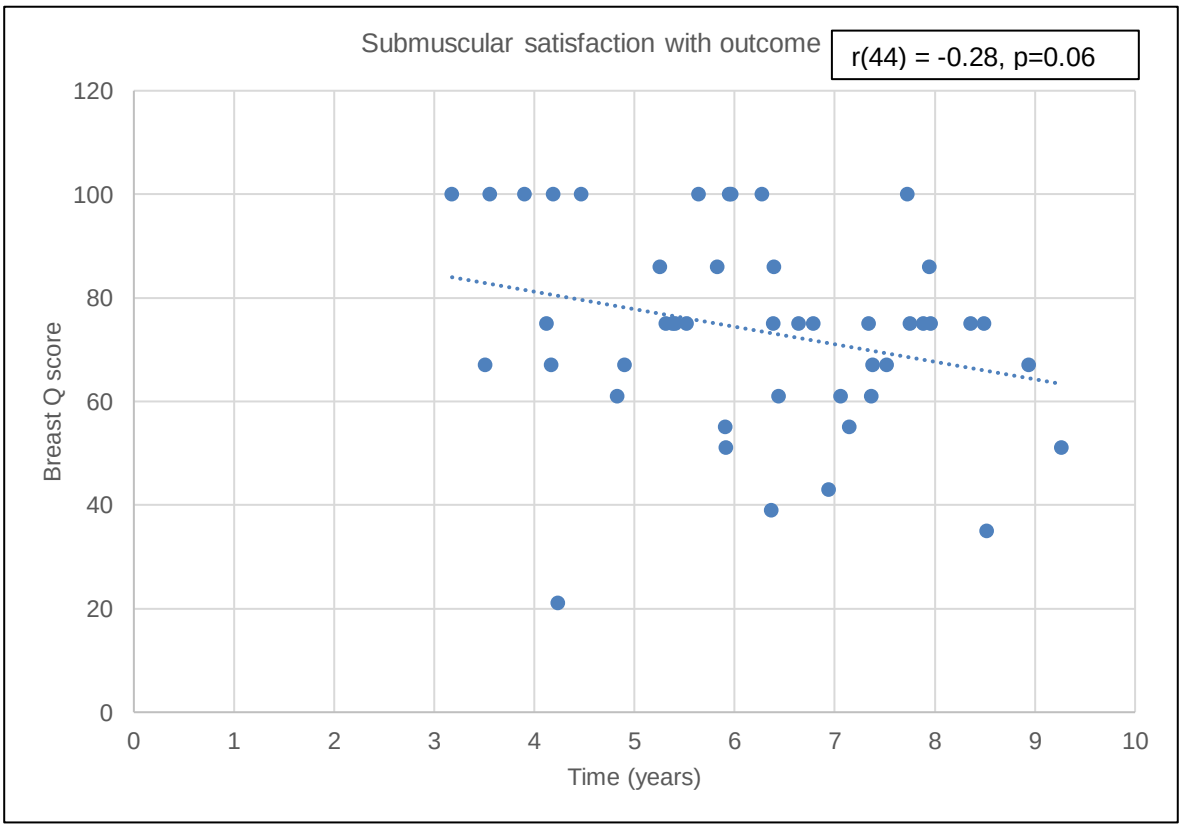
b.


Submuscular satisfaction with breasts
r(44) = -0.29, p=0.05
Breast Q score
Time (years)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
10

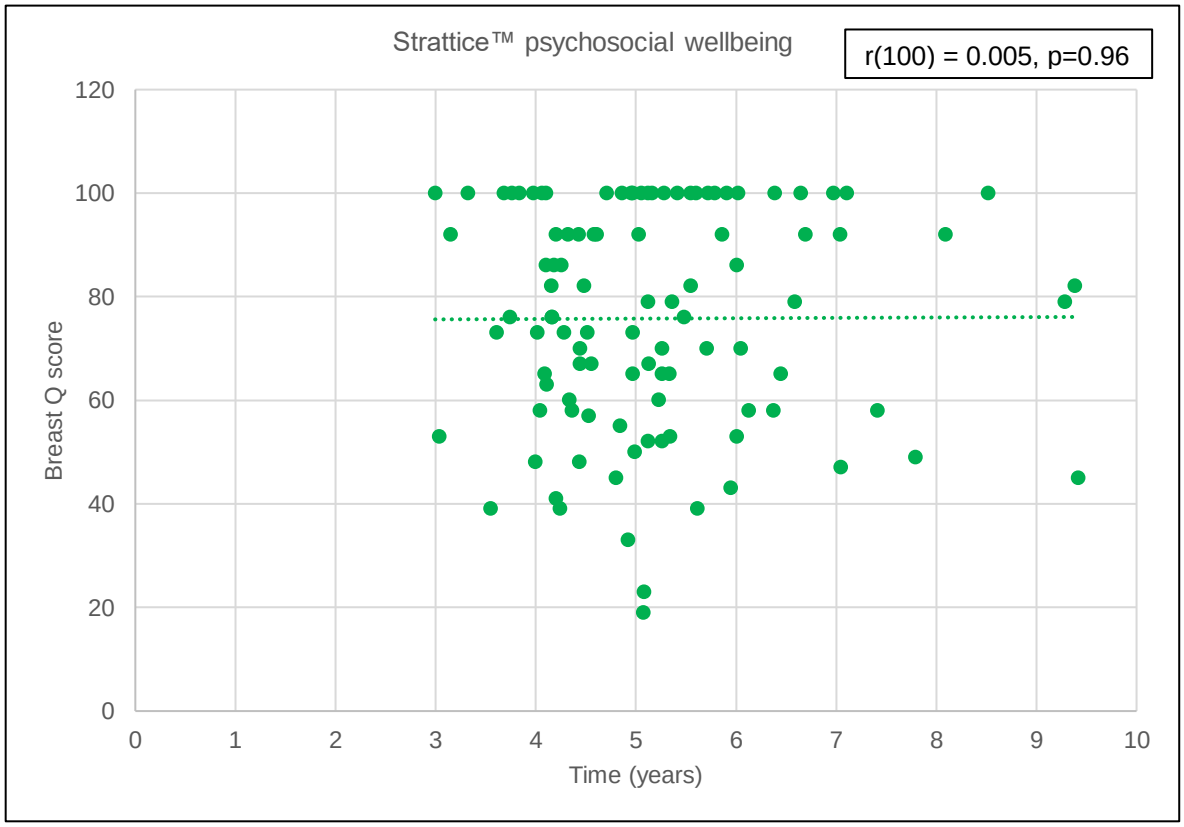
c.


Strattice™ satisfaction with outcome
r(98) = 0.05, p=0.65
Breast Q score
Time (years)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
10

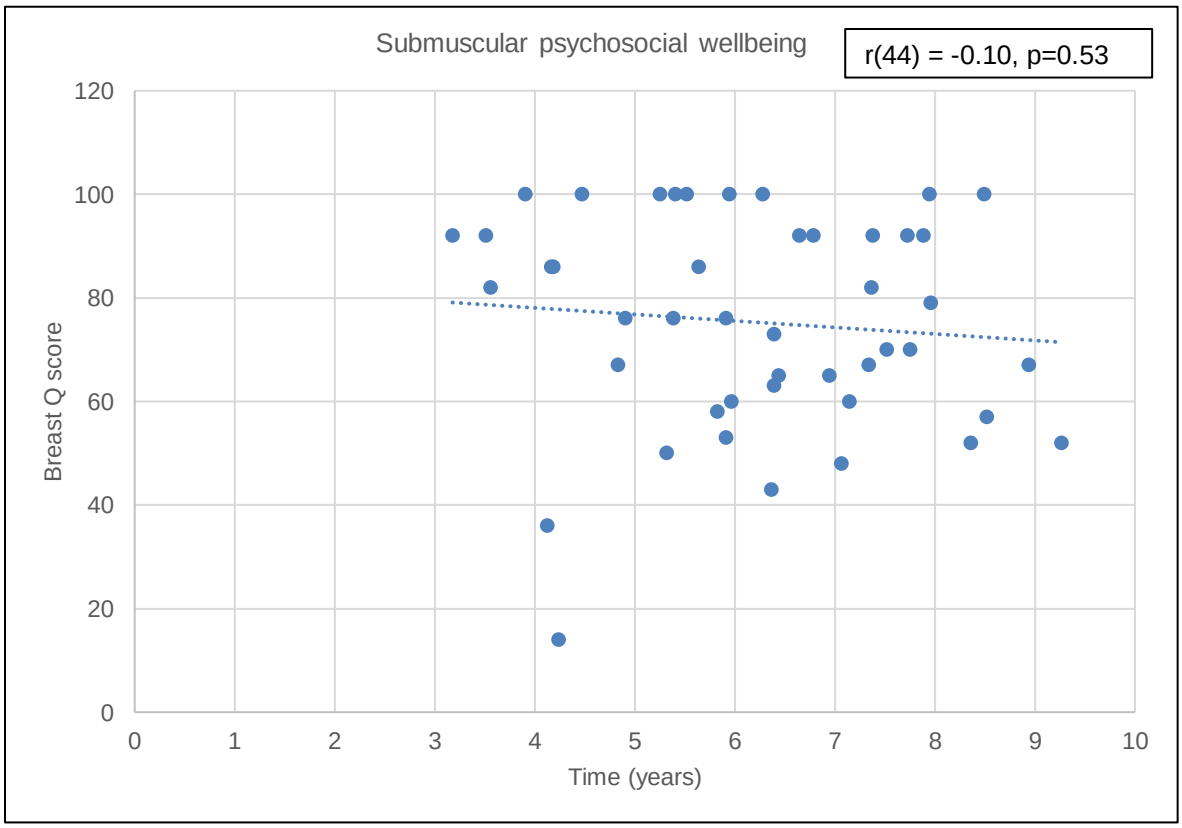
d.


Submuscular satisfaction with outcome
r(44) = -0.28, p=0.06
Breast Q score
Time (years)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
10

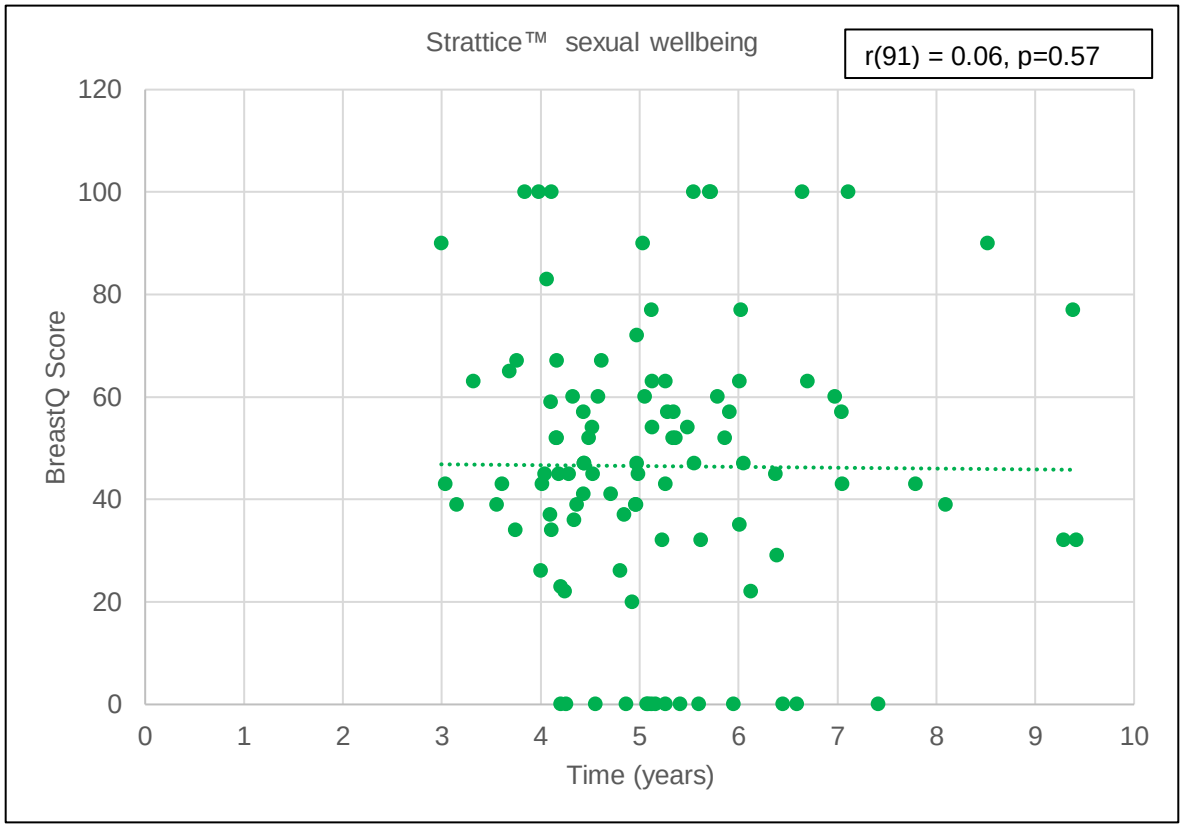
e.


Strattice™ psychosocial wellbeing
r(100) = 0.005, p=0.96
Breast Q score
Time (years)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
10

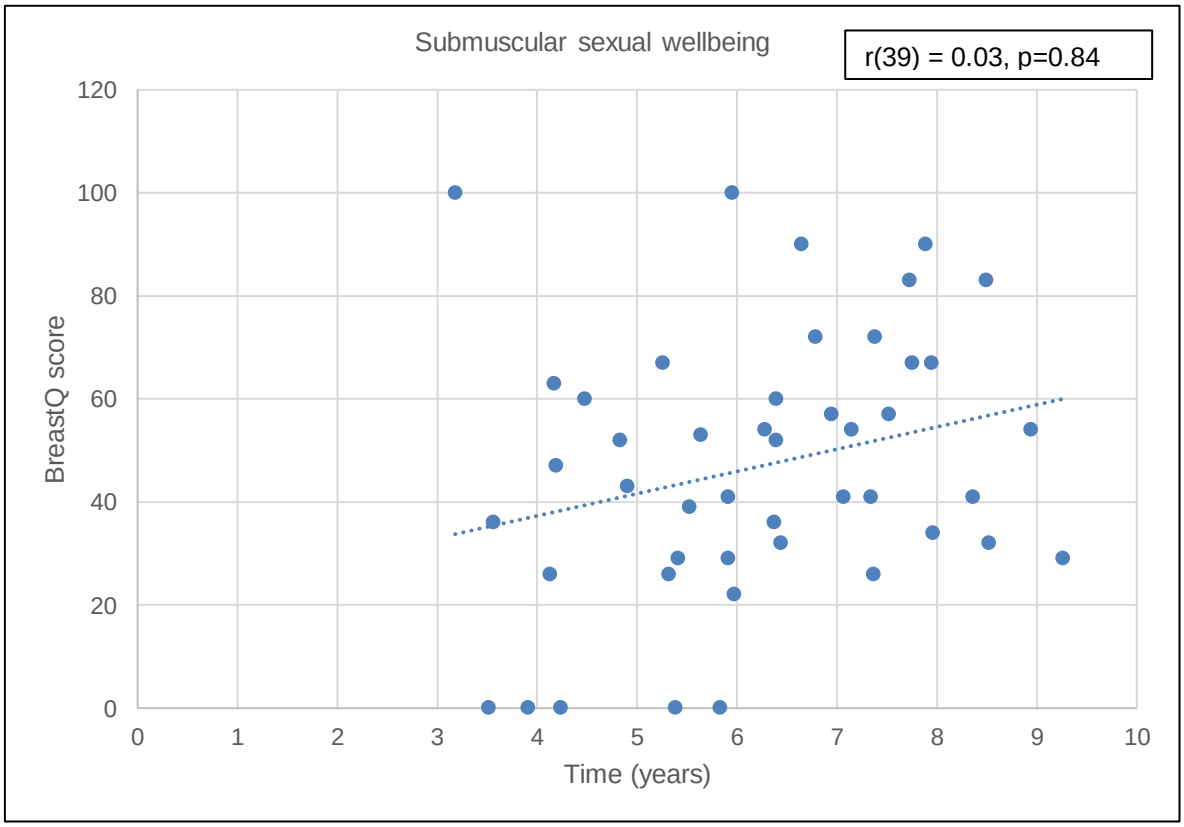
f.


Submuscular psychosocial wellbeing
r(44) = -0.10, p=0.53
Breast Q score
Time (years)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
10

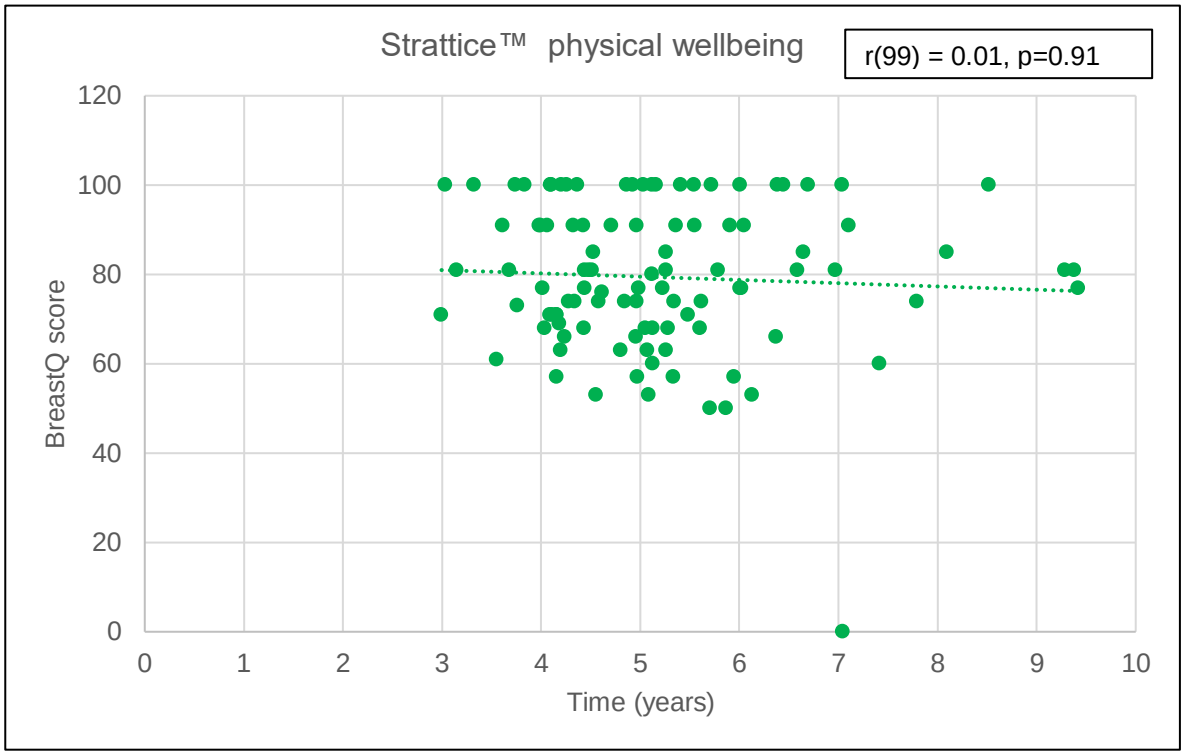
g.


Strattice™ sexual wellbeing
r(91) = 0.06, p=0.57
BreastQ Score
Time (years)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
10

h.


Submuscular sexual wellbeing
r(39) = 0.03, p=0.84
BreastQ score
Time (years)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9
10

i.



j.

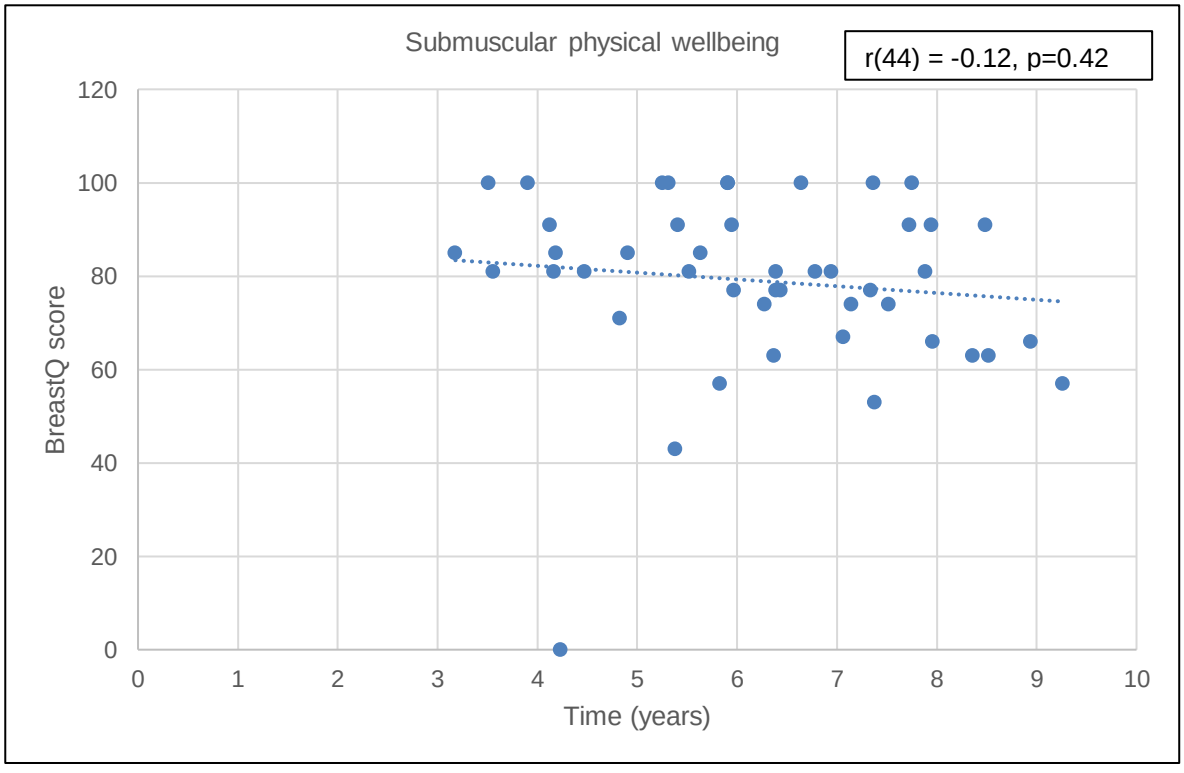


Figure 42 Breast-Q scores over time in Strattice™-assisted and submuscular reconstructions
Satisfaction with breasts **a.** Strattice™ reconstructions **b.** submuscular reconstructions,
Satisfaction with outcome **c.** Strattice™ reconstructions **d.** submuscular reconstructions
Psychosocial well-being **e.** Strattice™ reconstructions **f.** submuscular reconstructions
Sexual wellbeing **g.** Strattice™ reconstructions **h.** submuscular reconstructions
Physical wellbeing **i.** Strattice™ reconstructions **j**. submuscular reconstructions
Statistical analysis performed using Pearson's Correlation Coefficient

Comparison of BREAST-Q score per centre for Strattice™-assisted reconstructions

There were 62 completed BREAST-Qs from Centre 1, 11 from Centre 2 and 33 from Centre 3. There were no significant differences in median scores between the centres in any domain of the BREAST-Q (Figure 43).

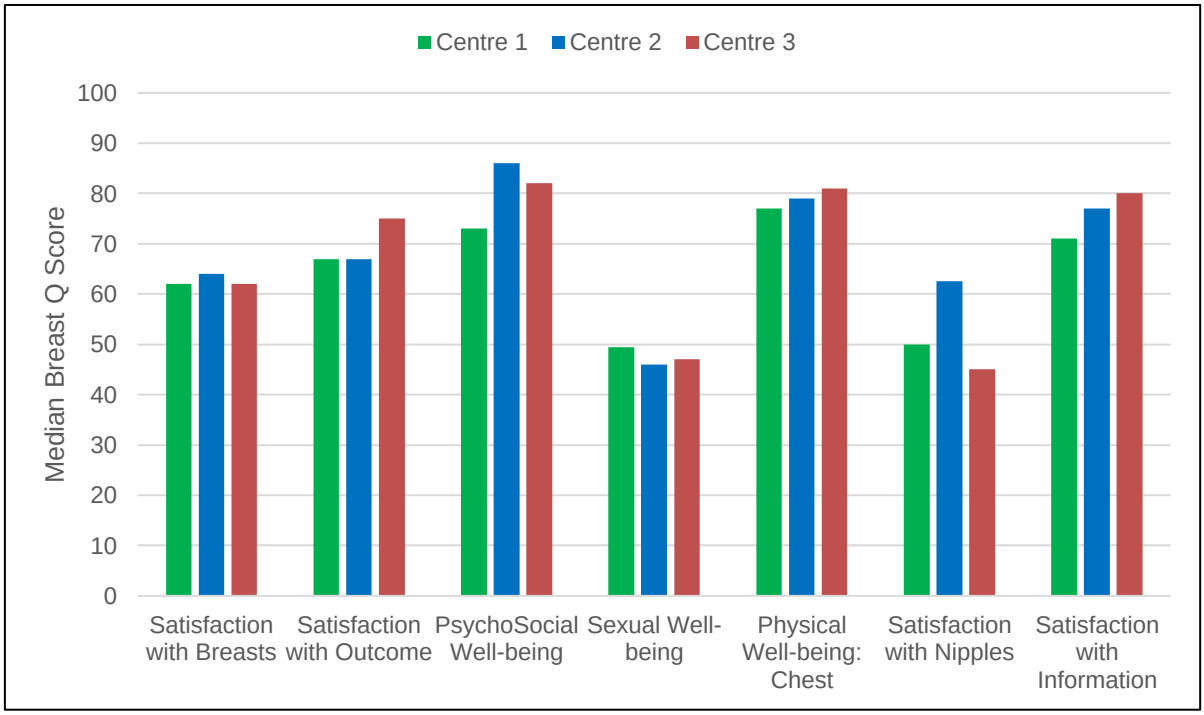


Figure 43 Comparison of median BREAST-Q scores per Centre in Strattice™-assisted reconstructions

Comparison of BREAST-Q score between those undergoing mastectomy and reconstruction for therapeutic versus risk reduction

There were 16 completed BREAST-Qs from patients who had bilateral risk reducing mastectomy and reconstructions in the Strattice™-assisted group and 7 in the submuscular compared to 90 and 40 for those that had one or both reconstructions for therapeutic reasons in the Strattice™-assisted and submuscular group respectively. There was no difference identified between median BREAST-Q scores in any domain when comparing the therapeutic and risk reduction reconstructions (Figure 44).

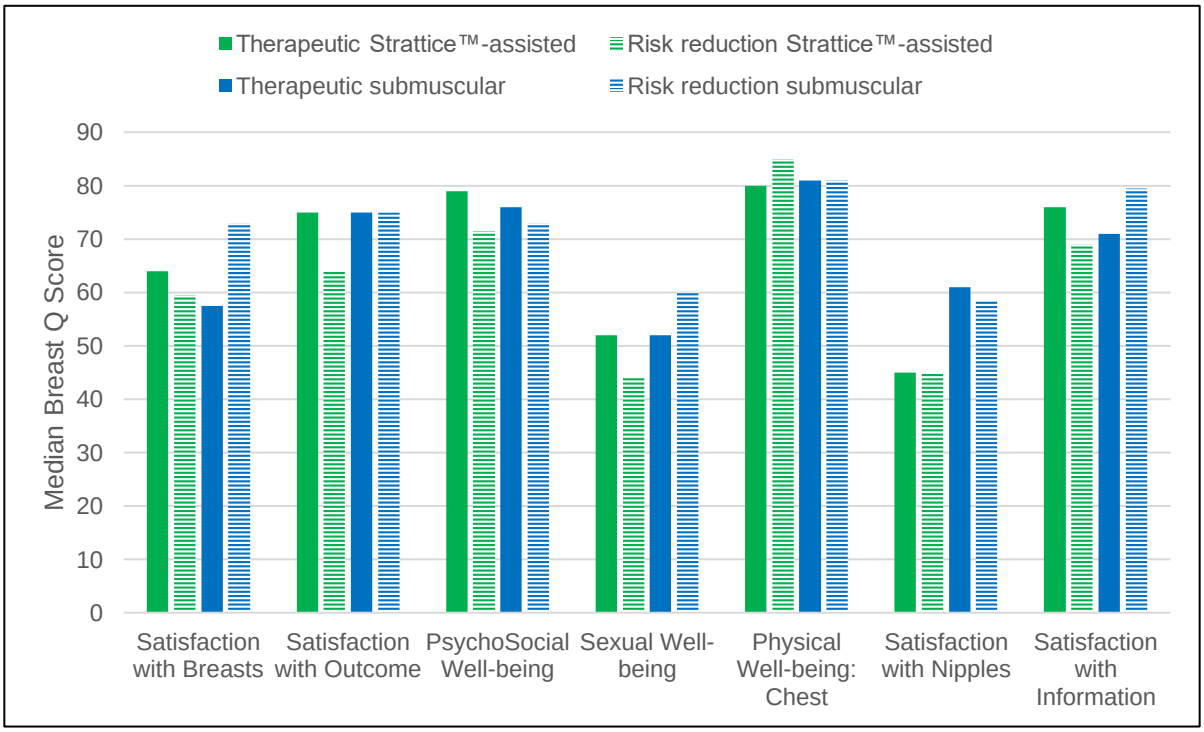


Figure 44 Comparison of median BREAST-Q scores in those undergoing Strattice™-assisted and submuscular reconstructions for therapeutic and risk reduction reasons

Comparison of BREAST-Q scores between those undergoing bilateral mastectomy and reconstruction and unilateral mastectomy and reconstruction

There were 61 completed BREAST-Qs from patients who had bilateral mastectomy and reconstructions (45 in the Strattice™-assisted group and 16 in the submuscular) compared to 90 from those that had unilateral reconstructions (60 in the Strattice™-assisted group and 30 in the submuscular group). There was no difference identified when comparing unilateral and bilateral reconstructions in total and within reconstruction type in any domain of the BREAST-Q.

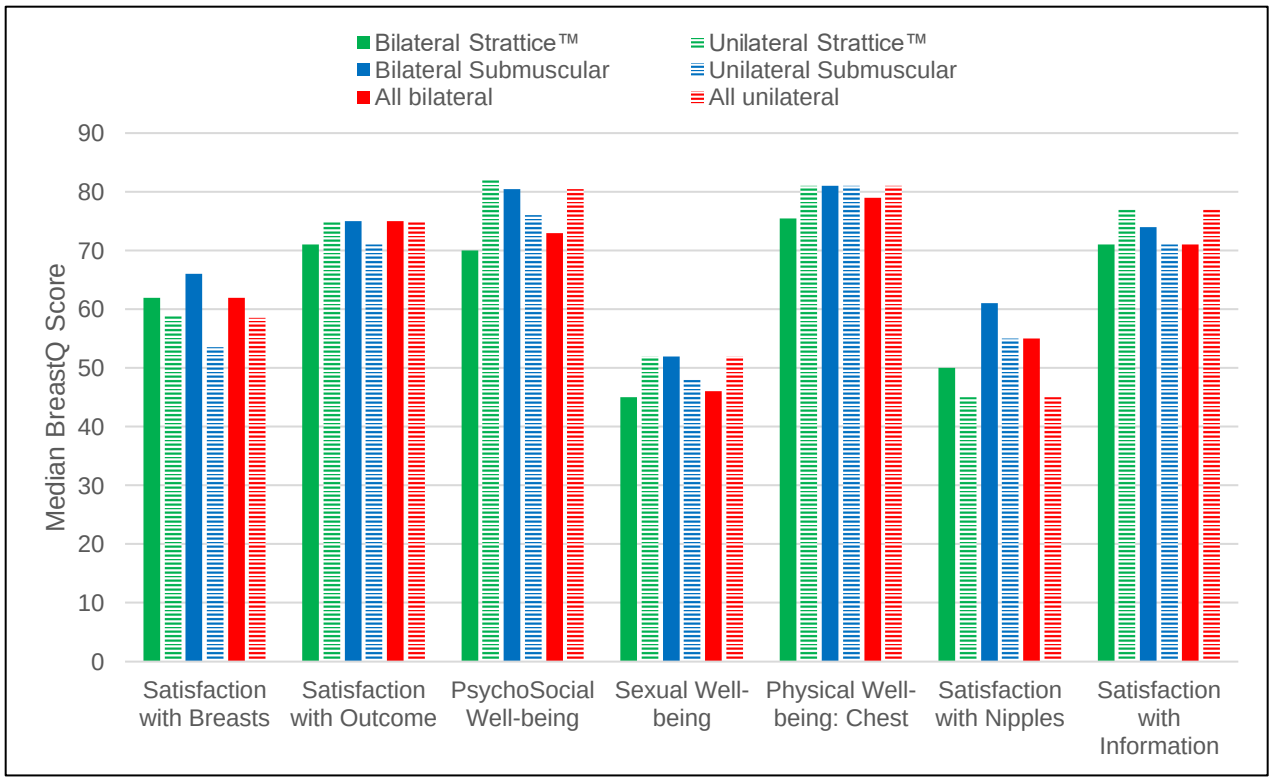


Figure 45 Comparison of median BREAST-Q scores in those undergoing unilateral and bilateral Strattice™-assisted and submuscular reconstructions

Comparison of patient reported satisfaction with breasts using BREAST-Q and surgeon reported general satisfaction score

There was a weak but significant positive correlation with patient reported satisfaction with breasts and surgeon reported aesthetic general satisfaction score in both the Strattice™-assisted (r(94)=0.39, p=<0.001) and submuscular reconstructions (r(39)-0.33, p=0.03).

3.3 Discussion

Through a combination of retrospective data collection and clinical assessments this multi-centre study has established an incidence of capsular contracture in implant based breast reconstruction with and without the use of Strattice™, with the longest median follow-up in published literature. Although it did not quite reach statistical significance a decrease in capsular contracture of almost 10% with a Strattice™-assisted reconstruction is of clinical significance and potentially important to patients. This is the first multi-centre study with a blinded independent assessment of capsular contracture in Strattice™-assisted reconstructions with a submuscular reconstruction control arm.

3.3.1 Demographics

The multi-centre nature of the study removes the bias of single-centre studies but also introduces significant variance in patient selection, technique, follow-up management etc. Across the three centres, 22 surgeons performed varying numbers of reconstructions within one or both groups and it is impossible to adjust for this. Except for age and smoking status, the two cohorts were otherwise well matched for pre-operative risk factors. There were significantly more younger women in the Strattice™-assisted group which may be accounted for by the higher rate of risk reducing surgery in this group or naturally younger women are likely to have less co-morbidities therefore deemed more suitable to use an ADM. An adequate blood supply to the mastectomy skin flap is essential for integration of the ADM (215) therefore the significant reduction in smokers in the Strattice™ group is likely a reflection on the known impact smoking has on the microvasculature system (251). Current practice remains, in certain units across Europe, to abstain from using ADMs in smokers. Despite higher stage disease in the submuscular cohort there was no difference in the percentage of patients receiving adjuvant radiotherapy which is a risk factor for capsular contracture. As expected with higher stage disease and more HER2 positive disease more patients received adjuvant chemotherapy and Herceptin in the submuscular group. There may have been selection bias in this subgroup with the operating surgeons perceiving these patients to be higher risk and therefore not offering a Strattice™-assisted reconstruction.

3.3.2 Post-operative complications

The rate of suspected infection was higher in both groups than the pooled analysis in the meta-analyses published comparing ADM-assisted reconstruction and submuscular techniques (252, 253) but lower than those published from the iBRA study and NMBRA (12, 238). The definitions used mirrored those in the iBRA study to ensure a meaningful comparison could be made. The Clavien-dindo classification, a widely accepted scale for grading surgical complications, although not specific to breast, was not used for this study due to its limited use in published breast literature (254). The results raise the concern of a higher infection rate in the Strattice™-assisted group however there are number of reasons why this should be interpreted with caution. Any redness or potential sign which required treatment with antibiotics was classed as infection which could have led to an over-estimation.

Red breast syndrome is a recognised problem with ADM use which is believed to be an immune reaction but can mimic signs of infection. A number of patients in this study were documented as having red breast syndrome but were treated with antibiotics as a precaution and therefore included as having a potential infection. Interestingly in the Strattice™-assisted group unlike the submuscular, having a known risk factor for infection did not impact whether you were treated for suspected infection or not suggesting patients may have been over cautiously treated in this group. There were 22 consultant surgeons performing the reconstructions, not accounting for the other doctors and nurses in their team who also reviewed and followed up the patients, all of who will have a different threshold to treat with antibiotics. This study was not powered to detect a difference in rate of potential infection between the two groups. The only reliable way to detail true infection rates would be performing a prospective study with a detailed criterion for infection however this would be very difficult and expensive to run.

As in the BRIOS and MROC study (223, 255) there was a significantly higher rate of wound dehiscence in the Strattice™-assisted group. Subsequently this lead to a higher implant loss rate secondary to wound dehiscence although the overall explantation rate was not significantly different between the two groups. The overall rate of wound dehiscence in the Strattice™ group (16.3%) was higher than that reported in the BRIOS study (9%) where Strattice™ was also used (223) and the MROC study (3.4%) where an unknown ADM was used (255). I would hypothesise an inherent bias in the wound dehiscence rate due to the importance of detecting, documenting and acting on even the smallest dehiscence in a Strattice™ reconstruction to prevent infection whereas with submuscular coverage the concern over a small dehiscence is less. Our definition matched that of the iBRA study to allow a more meaningful comparison however the specific rates of wound dehiscence have not yet been published. The majority of papers including the meta-analyses published comparing ADM and submuscular reconstructions comment on skin flap necrosis and although there may be a degree of necrosis at the wound edges instigating the dehiscence, this really is a different entity and cannot be used to compare to our data. The rates of skin flap necrosis were lower in both groups than published in the meta-analyses (224, 225, 227, 229, 252) but similarly found no difference between the two groups. Our data does raise concerns of higher rates of wound dehiscence in ADM reconstruction but due to the limitations of the study which include retrospective data and the study not powered for this complication it must be interpreted with caution. As with infection rates the most effective way to determine true rates of wound dehiscence would be with a prospective study.

Almost 50% of implants in the Strattice™-assisted group subjected to wound dehiscence were salvaged by returning to theatre. Other management strategies such as negative pressure wound therapy (256) have been suggested in the literature to potentially salvage ADM –assisted implant reconstructions. In our cohort 23 Strattice™-assisted reconstructions had a negative pressure dressing placed immediately post-operatively and four (17.4%) had wound dehiscence requiring return to theatre. However, it is unknown how many of those with a conservatively managed wound dehiscence involved the use of negative pressure wound therapy.

The presence of seroma was no different between the Strattice™-assisted and submuscular reconstructions which contradicts published literature (225-227). Aspiration of seroma was higher in the submuscular group. In the UK, when ADM assisted reconstructions were first introduced the accepted protocol was to insert two post-operative drains, one in the implant pocket and one between the skin and ADM, for two weeks. This prevented seroma fluid separating contact between the ADM and skin, improving/allowing prompt integration. Drain use protocols are not detailed in the current literature reporting an increase in seroma. Our longer drain use in the Strattice™- assisted group may account for the equivalent rates of seroma between the two groups. From approximately 2013 drains began to be removed at earlier time points, similar to those in the submuscular group and only one drain was used. However, data per year demonstrated equivalent seroma rates. Alternatively, seroma rates may not be related to the reconstructive procedure but the mastectomy therefore you would expect equivalence between the two groups. Formation of seroma remains poorly understood and although there are a number of identified factors the true pathophysiology is unclear. One of the techniques to reduce seroma formation is to remove the dead space it forms in (257, 258). In the Strattice™- assisted group inserting a fixed volume implant or expander implant filled this space hence reducing the space it could accumulate in and reducing the amount formed. Increase in back pressure from a tighter skin closure over a fixed volume implant and from the implant against the chest wall may decrease leakage of fluid from the tissues. The time points at which the seromas were drained was not collected but would have been useful in further analysis.

There were no differences in explantation rates secondary to post-operative infection or wound dehiscence between Strattice™-assisted and submuscular breast reconstructions which compares favourably to meta-analyses published (225, 229). The unplanned explantation rate in the Strattice™-assisted group matches that reported in the iBRA study (205) for all implant based reconstructions (n=2081) and for those performed with a biological mesh. However, the iBRA study reports at 3 months follow-up and only 50% of the 8.5% Strattice™-assisted explantations in this study occurred within the first three months. Patients and clinicians should be aware that the risk of explantation continues over two years post-operatively with a Strattice™-assisted reconstruction whereas with submuscular coverage there were no implant losses beyond nine months. There are no other studies detailing time to implant loss to compare to. The explantation rate secondary to post-operative complications in the Strattice™-assisted group are higher than the National Quality Criteria for breast reconstruction (<5%)(259) although marginally lower than those reported in the NMBRA (12). Within this study the explantation rates for submuscular reconstruction almost meet the criteria but given the variation in numbers performed in the three recruiting centres this result may be skewed and non-representative of the real-world. Conversely it demonstrates low levels of explantation can be achieved albeit in a specialist tertiary centre performing high volume implant based breast reconstruction.

Having a risk factor (smoker, very recent ex-smoker, diabetes or very low or high BMI) was not significant in whether you were treated for suspected infection or wound dehiscence in the Strattice™-assisted group but it was in the submuscular group. Risk factors were a significant predictor of unplanned explantation in both the Strattice™-assisted and submuscular reconstructions. This may reflect the over cautiousness or more aggressive treatment in the Strattice™-assisted group. However, as previously discussed the study was not powered for post-operative complications and with multiple testing could result in both type I and II errors.

After unplanned explantation, significantly more women in the Strattice™-assisted group pursued further reconstruction than in the submuscular group. This differed to that reported in the BRIOS Study however their numbers were much lower, four submuscular reconstructions who all underwent further reconstruction (260). It is impossible to appreciate the reasons for this from our study. There is a paucity of literature on outcomes after failed implant based breast reconstruction and what influences patient decisions in this situation. The results of the LiBRA (Loss of implant breast reconstruction evaluation) study will hopefully improve on this (261).

The reasons for higher rates of infection and unplanned explantation are unclear. Potentially best practice guidelines are not being adhered to (262, 263) or poor patient selection. However, it is clear that these outcomes need to be improved and there are many factors and techniques which should be considered when performing implant based reconstruction (264). It has been proven following a checklist prevents serious untoward incidents occurring, reducing morbidity (265). Following the evidence based TIC checklist (264) may reduce breast implant associated infection and therefore unplanned explantation and other long-term sequelae of infection. Achieving the low levels of implant infection and failure (1%) of our orthopaedic colleagues (266) is something to aim towards.

Return to theatre rates secondary to a post-operative complication (haematoma, infection or wound dehiscence) were higher in the Strattice™-assisted group, significantly for wound dehiscence, however this did not infer a higher implant loss rate. Our rate of 18.3% was lower than that reported in a recent randomized control trial comparing Strattice™ and a submuscular technique (223), however this trial was stopped prematurely due to high complication rates in the Strattice™ arm and came under significant criticism (267, 268). Unfortunately, other large prospective cohort studies have not reported their return to theatre rates to compare to. The rates in this study were equivalent to those reported in the iBRA study for biological mesh, however they only reported up to three months post-operatively (205). The rate was triple of that reported by the NMBRA in 2011 (12). I would suggest the increase in return to theatre has not been seen due to an increase in complications but due to a change in practice. Taking a more aggressive approach in to the management of post-operative complications is likely to result in a more favourable overall outcome as demonstrated in other studies of implant based reconstructions (269). In the Strattice™-assisted group 50.5% of those returned to theatre lost the implant compared to 80% in the submuscular group. The threshold of individual surgeons to take a patient back to theatre cannot be accounted for in this study.

However, the surgeons that were performing the majority of the submuscular reconstructions were not performing any of the Strattice™-assisted reconstructions so it could be hypothesised they had a higher threshold for return to theatre therefore the submuscular reconstructions were in less of a salvageable condition when they did return to theatre hence the higher loss rate in this subgroup.

The major limitation with the complication data is retrospective collection. Although data was meticulously collected from several sources to ensure accurate and complete data sets, certain variables may not have been recorded at the time of the event potentially leading to under reporting. Conversely it may be difficult to assess the degree of the complication e.g. infection, hence any use of antibiotics being a marker of suspected infection, leading to over reporting. The three centres recruiting to the study were significantly different in proportion of reconstructions they performed in each group, which may skew the data. Centre Three had a higher suspected infection rate and unplanned explantation rate in the Strattice™- assisted group compared to Centre One. They performed only 2% of the submuscular reconstructions so it is difficult to extrapolate true rates from such small numbers. It is possible that they would have equally as high a complication rate in the submuscular reconstructions should they have been performing them therefore altering the overall data significantly for this group.

The effects of the learning curve are well recognised (222) and were potentially observed in this study. However, after the initial reduction in implant loss rates over the first two years, proposed as the learning curve effect there was a further rise in implant loss rates. Potentially the strict criteria for performing ADM-assisted reconstructions was relaxed and this increase was due to the fact that higher risk patients were under-going the procedure (270).

This study was conducted in the three centres performing the highest number of Strattice™-assisted breast reconstructions in the North of England however there is still a wide variation in outcomes e.g. implant loss rates 7.2%, 10.9% and 12.4% and suspected infection rates of 18.3%, 14.6% and 26.2%. It demonstrates good outcomes can be achieved but also raises concerns that even despite the substantial experience of a centre, the outcomes are still not as good as what have been achieved in other centres. How can this be improved? Should low volume units with less experience be introducing the technique? Is it surgeon/technique related? Should there be more rigorous training or review of people performing the procedure? Or is it patient selection? Different populations, different risk factors? These are all questions which remain unanswered with regards to ADM-assisted breast reconstruction which although a relatively new technique has been performed for over 10 years in the UK. Addressing these factors may improve outcomes for patients undergoing this and other new techniques in breast reconstruction.

3.3.3 Capsular contracture

Our rate of capsular contracture (13.6%) in the Strattice-assisted group is higher than that reported in the literature (<10%) however they have much shorter follow-up (0.6 – 2.4 years) and the majority of studies include reconstructions using human ADM which is not licenced for use in the UK (253). The largest published case series (249) with a mean follow-up time of 4.7 years also reports a lower rate of capsular contracture however, this was single centre, predominantly human ADM and the operating surgeon reported the outcomes. Using the same case series but comparing to their cohort of Strattice™-assisted reconstructions there were no incidents of capsular contracture in the mean follow-up period of 3.5 years (247). The rate of 21.2% in the submuscular group compares to rates reported in the core studies (155, 162, 163). The core studies also used Baker grade however were reported by the operating surgeon who gained financially for participating in the study and with lower numbers of reconstruction subjects enrolled than specified in the protocol.

In this study, the same blinded independent researcher examining all of the patients leads to less bias than operating surgeon reported outcomes. 40% of patients who had undergone either a Strattice™-assisted or submuscular reconstruction were recruited. This was an adequate sample size from our initial power calculation to have 80% power to detect a difference at the 2-sided 5% significance however there is still the possibility of over or under reporting of capsular contracture. The patients willing to participate could be either the highly satisfied or dissatisfied leading to over/under reporting.

The numbers in each group were too small to perform a univariate or multivariate analysis for risk factors for capsular contracture (infection, haematoma, radiotherapy). In the Strattice™-assisted group there was no difference in the rate of capsular contracture after a post-operative complication however in the submuscular group, the rate of capsular contracture was much higher (9.1 vs. 33.3, p=0.0326) after a complication had occurred. We could hypothesise that Strattice™ does have a protective role in the presence of other risk factors.

Using Baker grade (164) to assess for capsular contracture is widely accepted but subjective. To reduce the subjectivity and bias the same person examined each participant and was blinded as to the type of reconstruction. To add an objective measurement to the assessment of capsular contracture tonometry was used. Tonometry has been found to have a good correlation with Baker grade however in our study there was weak correlation between increasing baker grade and decreasing tonometry values. No significant difference was found between the tonometry readings of the two reconstruction types, no further studies have compared tonometry readings between reconstruction types. Other variables may impact the firmness of the breast that may not be a result of changes to the capsule. There was a weak correlation between increasing BMI and increasing tonometry value, however the cause is unclear, it maybe that skin flap thickness has an impact on the reading. An animal study reporting increased tonometry readings after lipofilling would support this hypothesis (169).
We suggest tonometry would be a more sensitive tool for the assessment of capsular contracture when serial measurements are taken of the same breast during the follow-up period.

There was a significant reduction in revision surgery for capsular contracture in the Strattice™-assisted group which also supports my hypothesis that there is a lower incidence of capsular contracture in Strattice™-assisted reconstructions.

The revision rates were equivalent between the two groups during the total follow-up period however the revision rate at five-years was significantly higher in the Strattice™-assisted group compared to submuscular. The average revision rates in these two groups of 44% is similar to those extrapolated from the core studies of 35-40% (46, 155, 156, 158-163) but higher than a recent retrospective study comparing the same two groups (230). This may be attributable to many factors such as learning curve affect in the Strattice™-assisted group, surgeon's willingness to offer revision surgery and ultimately patient preference which cannot be accounted for in a retrospective study. The difference in revision rates between the three units in this study demonstrates variation within the same reconstruction type also again for reasons as above which cannot be accounted for in this study. However, a significant limitation is the difference between the numbers of the two types of reconstructions performed within the three centres, a significantly lower rate of submuscular reconstructions at centre two and three may skew the data. The higher revision rates seen in the Strattice™-assisted reconstructions may well have been mirrored in the submuscular reconstructions had they been performing them. Patients may also undergo revision procedures in a different unit to where their initial reconstruction was performed potentially increasing the rate further as it was not possible to capture this data in this study.

3.3.4 Aesthetic outcomes

This study has compared aesthetic outcomes between ADM-assisted and submuscular reconstructions with the longest follow-up to date. The general satisfaction score (1-10) is significantly higher in the Strattice™-assisted group from all three assessors supporting improved aesthetic outcome as one of the major benefits of ADM-assisted reconstruction. Specifically reports of improved lower pole projection and inframammary fold definition (31, 63, 206-211) are supported by a significantly higher score in the breast volume and breast shape domains of the aesthetic scoring across all three assessors. Other retrospective studies with a maximum mean follow-up time of 1.7 years also detected a significant overall improvement in aesthetic outcome with ADM use and specifically in the domains of breast mound volume, placement and inframammary fold (232) and contour and implant placement (231). The only RCT performed comparing Strattice-assisted and submuscular reconstructions reported no difference in aesthetic outcome however this was at 1 year only and it is widely accepted that aesthetic satisfaction declines with time in implant based reconstruction without ADM (233). The aesthetic assessment in this study was taken at a single time point for each participant but there were a wide range of follow-up times (three years to 9years and five month).

Interestingly there was a very weak negative correlation of score with time in the Strattice™-assisted reconstructions and very weak positive correlation of score with time in the submuscular group (who had no revision surgery during the follow-up period) across all three assessors, none of which were significant. There are no studies reporting on change in aesthetic outcome with time in ADM-assisted reconstruction to compare to.

To minimise bias the photographs were viewed on a PowerPoint in random order with blinded assessors who had no prior knowledge of the study or any additional information about the participants or their operative/post-operative course. The breast surgeon has almost 30 years of experience in breast reconstruction, the breast care nurse over 20 years and the lay person no experience of breast reconstruction. The major limitation to cosmetic assessment is there is no widely accepted validated tool. We used the 10 point Visser scale (62) as it scored most highly when compared by Maass et al. (60). This was also the same scale used in the BRIOS trial. The assessment remains subjective in nature. 15 random photographs were repeated to assess intra-rater agreement. Overall the breast surgeon and lay person had moderate reliability but the Breast care nurse had good reliability.

The mean aesthetic score from the breast surgeon in this study was higher in both groups than reported by the breast surgeons in the BRIOS trial when the same scale was used. The breast surgeon gave highest scores followed by the breast care nurse and lay person contrary to previously published aesthetic outcome studies (63). There was moderate reliability between the breast surgeon, breast care nurse and lay person (ICC 0.74) understandably they will have differing views given the range of their experience and knowledge. The surgeon is more aware of the limitations of implant based reconstruction and what is physically achievable. The breast care nurse has potentially seen a variety of results from both good and not as good surgeons bringing a different perspective. The presence of the NAC may have not affected the overall general satisfaction score for the surgeon or breast care nurse as they understand not all patients want to proceed to nipple reconstruction however this may have affected the score in a lay person as naturally they expect a breast to have a nipple.

There have been recent developments in computer programs to evaluate aesthetic outcomes using three-dimensional surface imaging, however this has been predominantly used in assessing outcomes after breast conserving surgery (271, 272). Tsay et al. performed 3D Mammometric comparison of implant-based reconstruction with and without ADM at early (1-3 months) and late (6-9 months) time points demonstrating a sustained significantly greater point of maximum projection and length of lower pole curvature in the ADM group (273).

Improved aesthetic outcomes perceived by surgeons do not necessarily correlate with improved patient satisfaction (260), which is the ultimate aim. However, in this study we did demonstrate a weak but significant positive correlation between patient satisfaction with breasts and surgeon reported aesthetic general satisfaction.

3.3.5 Patient reported outcomes

There were no significant differences found in any domain of the BREAST-Q when comparing the two reconstruction types which compares with the results of the BRIOS trial (260), comparing one stage Strattice™-assisted reconstruction and two-stage submuscular reconstruction. The BREAST-Q scores compare with those in the BRIOS trial in all domains except satisfaction with nipples where we have scored almost 30 points less. This is likely to reflect the time points at which the questionnaires were completed (mean of 17 months in the BRIOS and over 60 months in BROWSE) as the longevity of nipple reconstruction results are limited. Both groups had a mean score for satisfaction with breasts which fell within the reported range of BREAST-Q scores (55 – 71) for satisfaction with breasts in implant based reconstruction (274).

Using the minimally important difference of four points in the satisfaction with breasts and sexual well-being domain calculated by the authors of the BREAST-Q (275, 276) suggests that there is a clinically meaningful improvement in patient satisfaction with breast in the Strattice™-assisted reconstruction despite not being a statistically significant change. This would also suggest there is improved sexual well-being in the submuscular group. Without baseline pre-operative scores it is difficult to explain this.

This is the only study which compares long-term PROMs data between Strattice™-assisted (median follow-up time of five years) and submuscular (median follow-up time of six years four months) reconstructions. One study comparing PROs in human ADM-assisted reconstructions at a median time of 5 years (274) without a comparison to submuscular has equivalent BREAST-Q scores to our Strattice™-assisted group except in sexual wellbeing (10 point higher) and satisfaction with nipples (20 points higher). However, their cohort was over 50% prophylactic surgery therefore potentially have a higher number of nipple sparing mastectomy and reconstructions. Studies demonstrating higher BREAST-Q scores in ADM reconstructions gained the PROMs data at a much shorter median time suggesting the reported improvements in quality of life may be short lived. These studies did not directly compare with submuscular reconstructions. Reasons for the short-term improvements could be reduced post-operative pain and one stage therefore no extra visits for expansion in ADM assisted reconstruction. This potentially further corroborates the low correlation between aesthetic score and quality of life scores i.e. once this stage has passed the longer-term differences which exist in ADM reconstruction e.g. improvements in aesthetics and reduced capsular contracture are not major determinants of quality of life. Interestingly there was a trend of reduced satisfaction with breasts, outcome and psychosocial well-being with increasing time in the submuscular group which was not demonstrated in the Strattice™-assisted group.

Although some studies have demonstrated complications negatively impact patient satisfaction (274, 277), complications had no impact on the BREAST-Q score in our cohort. There are a number of factors which may have influenced this such as the degree of complication, how the complication was managed and the revision surgery undertaken in order to maintain adequate patient satisfaction.

Other factors found to positively impact patient satisfaction e.g. bilateral surgery and prophylactic surgery were not found to show a significant difference in this cohort. Such sub-analyses create low numbers in each group and are not powered to detect a difference therefore must be interpreted with caution.

BREAST-Q is the most commonly used validated tool for PROMs in breast reconstruction and has found to be highly reliable and responsive (85). The BREAST-Q was completed at a single time point with no pre-reconstruction questionnaire previously completed. There are many factors which can affect domains such as sexual well-being and psychosocial well-being therefore having baseline scores would allow for a more robust interpretation. Despite having PROMs data from a wide range of follow-up times, we could make more accurate conclusions of the effect time has on PROMs by having the same cohort of patients completing the questionnaires at sequential time points. A prospective study with long-term follow-up would be a more suitable design to collect this data.

3.3.6 Sub-group analyses

Historically two-stage implant based breast reconstruction has been found to be safer than direct-to-implant (41, 278), however we found no difference in unplanned explantation rates or overall complication rates between the two techniques. Although our overall complication rate was higher in the total Strattice™-assisted group, I suspect this was secondary to the higher risk patients in the Strattice™-assisted group undergoing a two-stage procedure. More recent multi-centre data from the MROC study also demonstrated comparable outcomes between direct-to-implant (n=99) and two-stage reconstructions (n=1328), however the number of direct to implant reconstructions performed was significantly lower (279). Single centre retrospective cohort studies have shown improved outcomes in direct to implant reconstructions especially in selected patient groups e.g. BMI<30 (280) and in the presence of adjuvant radiotherapy (281).

In the Strattice™-assisted group the therapeutic mastectomy and reconstructions had higher incidence of suspected infection and seroma than the procedures performed for risk reduction. This differs to current literature, where no differences were found (247). Pre-operative risk factors were equivalent except for 7% in the therapeutic group underwent neoadjuvant chemotherapy. Axillary surgery, previously described as a risk factor for major complications after immediate reconstruction may account for this difference (282). Within the therapeutic group alone there was an increase in complication rate in those that underwent axillary surgery at the time of reconstruction compared to those that had either no axillary procedure or the axillary surgery prior to the reconstruction being performed. Other procedures such as previous wide local excision does not appear to have a significant impact.

Significantly more nipple sparing mastectomies were treated conservatively for wound dehiscence unlike in other case series where no difference was found between skin sparing (nipple sacrificing) and nipple sparing mastectomies (283, 284). Unfortunately, data was not collected on the time to heal or the site of the dehiscence i.e. nipple or remaining surgical scar.
75% of the wound dehiscence were in patients having the procedure for risk reduction and in those having a therapeutic procedure there were no incidences of delay to adjuvant treatment. However, it is something to consider when counselling patients who may require adjuvant treatment as other large cohort studies have demonstrated higher rates of complications in therapeutic nipple sparing mastectomy compared to skin sparing mastectomy (284).

The long-term (5 year) cost effectiveness was equivalent between the single stage Strattice™-assisted and two-stage submuscular reconstructions in our study. There is no other published long-term UK literature to compare to. In the Dutch BRIOS trial the overall cost was significantly greater in the single stage Strattice™-assisted reconstructions; however, their complication rate was higher than in our study and their mean follow-up time was only three years (285). Two American Studies projecting long-term costs in implant reconstructions based on local and published complications rates suggest single-stage human ADM reconstructions to be equivalent (286) or significantly cheaper (287) than two stage submuscular. Our analysis only covered costs of surgical procedures (index procedure, further planned and unplanned procedures) however there are other factors to consider such as hospital length of stay and clinic visits for conservative management of complications or expansion. A full health economic evaluation would be beneficial.

This study compares the outcomes of Strattice™, a porcine ADM however there are over 15 other porcine and bovine ADMs available on the UK market and a number of synthetic meshes. Data comparing outcomes between different ADMs is limited. The MROC Study, comparing four human ADMs, found a significant increase in overall complications and reconstructive failure in one ADM (288). A small study comparing Strattice™ and Surgimend™ (289) demonstrated significantly higher rates of skin erythema in the Strattice™ reconstructions only. This could be attributable to the variation in production and washing technique peri-operatively. The results from the iBRA study showed a higher complication rate in synthetic mesh compared to biologic mesh and submuscular (238). Unpublished data from Edinburgh of their ten-year experience performing over 700 mesh assisted immediate implant based reconstructions demonstrates comparative complication rates between ADMs however a significantly higher complication rate when using one particular synthetic mesh (270). Many ADMs are introduced to the UK market with minimal safety and long-term data. This study supports the use of Strattice™ with the most comprehensive short and long-term outcome data of all xenogenic ADMs.

The number of pre-pectoral reconstructions performed in this cohort was small so it was difficult to make any meaningful comparison. However, this technique has gained popularity in the past four years with centre one already performing over 500 pre-pectoral reconstructions. It would be useful to compare the short and long-term outcomes of pre-pectoral and sub pectoral Strattice™-assisted reconstructions.

Dermal sling and dermal sling with Strattice™ were excluded from the study as the numbers were small and we did not want too many variables and confounding factors but we appreciate both techniques are now common practice and comparative outcomes also need to be considered.

In summary, this study provides the most robust UK evidence that there is a reduced incidence of capsular contracture in Strattice™ reconstructions compared to a submuscular technique. However, the difference was not as great as expected. Although it appears more Strattice™ reconstructions are treated for suspected postoperative complications this does not transpire to a significant increase in implant loss or the most problematic long-term complication of capsular contracture. Other benefits of Strattice™ reconstruction include improved aesthetic outcomes.

4. Results: Capsule Study – a comparison of capsule in patients undergoing subpectoral breast reconstruction with implant and porcine acellular dermal matrix

4.1 Summary of methods

Patients who were undergoing revision surgery after implant-based reconstruction with Strattice™ were recruited to have biopsies taken from the native capsule, where the implant lay beneath pectoralis muscle and from the capsule associated with the ADM, where the implant lay beneath the Strattice™. The capsule was then analysed with histology and immunohistochemistry stains.

4.2 Study group demographics

Seven patients were recruited to the study (Table 31), five were bilateral cases who had both breast reconstructions biopsied. A total of 12 breast implant capsules were analysed. The original mastectomy and reconstruction was performed for risk reduction in eight of the capsules examined. Prior to this procedure where the biopsies were taken, two had undergone evacuation of haematoma after the initial reconstruction surgery and two had revision surgery to upsize the implants. Textured implants were used in 11 cases and polyurethane in one. No reconstruction received adjuvant radiotherapy.

Table 31 Patient demographics of the seven patients recruited to the Capsule study, comparing the capsule in patients with a sub-pectoral breast reconstruction with implant and Strattice™

	n=7
Mean age [range] (years)	43 [33 – 62]
Mean BMI [range]	24.2 [19.5 – 30.2]
Smoking status	
Smoker	0
Non-smoker	7
Diabetes	0
History of abnormal scarring	0
Previous chest wall radiotherapy	0

The current procedure where biopsies were taken was the planned second stage of reconstruction (exchange of tissue expander for fixed volume implant) in five breasts and a revision procedure in seven (five for animation and two for patient request to upsize). The median time from their last procedure was six months (range five – 81.5 months) (Table 32). The participants were examined on the day of the procedure, ten reconstructions had a Baker I capsule and two a Baker II capsule (164). The mean tonometry reading was 5.8 (range 5.1 – 6.4) for the Baker I capsules and 5.2 (range 4.3 – 6.1) for the Baker II capsules.

Table 32 Implant data per patient. Implant duration is the time from previous surgery (where current implant was inserted) to current procedure (where the biopsies were taken as part of the Capsule Study)

Patient Number (laterality)	Implant inserted with Strattice at original subpectoral reconstructive surgery Type (brand)	Implant inserted during further revision surgery prior to capsule biopsies taken	Implant duration (months)
1 (B/L)	Textured TE (Nagor™)	N/A	6
2 (B/L)	Textured TE (Nagor™)	N/A	6
3 (B/L)	Textured implant (Nagor™)	N/A	54
4 (B/L)	Textured implant (Nagor™)	N/A	6
5 (R)	Textured TE (Allergan)	N/A	5
6 (B/L)	Textured Becker (Mentor®)	Textured implant (Nagor™)	81
7 (R)	Polyurethane implant (Silimed®)	N/A	24

B/L= bilateral, R= right, N/A= not applicable

4.3 Comparison of native capsule with ADM capsule using histology

All analysis was performed within the three layers of the capsule, demonstrated in figure 46 and described in detail on page 35. Tissue beyond this e.g. subcutaneous fat or muscle if present was not analysed.

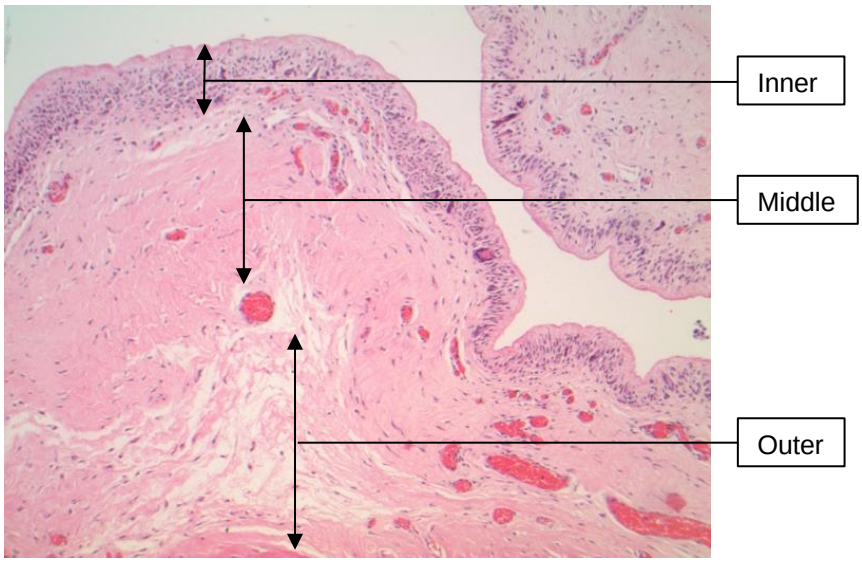


Figure 46 Representative image of breast implant capsule demonstrating the three layers of the capsule where analysis was performed. Inner layer, surface in contact with the implant, a thin synovial-like metaplasia, middle layer highly cellular with internal vascular supply and outer layer of connective tissue rich in collagen fibres

4.3.1 Haematoxylin & Eosin staining

Fibrosis

The extent of fibrosis, defined using H&E staining as eosin (pink) stained stroma was scored on a scale of 0 (none), 1 (mild density <25%), 2 (moderate density >25% - 75%) and 3 (severe density >75%), based on the density of fibrous compared to non-fibrous stroma such as fat. Thickness (mm) of the fibrosis was also measured.

The extent of fibrosis was less in the native capsule (mean 1.79 ± 0.14 (SEM)) than the ADM capsule (mean 2.79 ± 0.11 (SEM)), p<0.001. The thickness of fibrosis was also lower in the native capsules (mean 1.72mm ± 0.2 (SEM) vs. 3.61mm ± 0.78 (SEM), p=0.02) (Figure 47).

a. **b.**

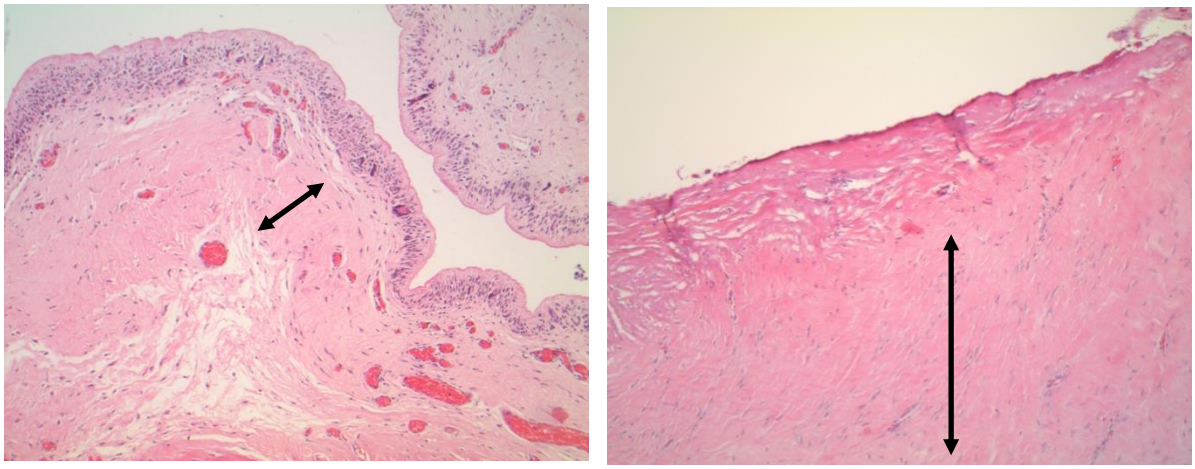


Figure 47 Photomicrographs of H&E staining demonstrating extent of fibrosis, comparing (a) native capsule, score 2, 2.5mm with (b) ADM capsule, score 3, 11mm. Magnification x100 (*surface in contact with implant) Black arrows indicating the area of fibrosis.

Inflammation

Inflammation, defined as the presence of acute (neutrophils) or chronic (lymphocytes, eosinophils, macrophages and multinucleated giant cells) inflammatory cells was scored on a scale of 0 (none), 1 (mild – few scattered inflammatory cells with space between each cell), 2 (moderate – increased numbers of inflammatory cells with some areas of densely packed inflammatory cells but adjacent areas of inflammation having space between the inflammatory cells) and 3 (severe – densely packed inflammatory cells with little intervening stroma between cells).

Perivascular inflammation, defined as presence of inflammatory cells surrounding blood vessels was also scored on the same scale as above.

There were no acute inflammatory cells identified in either the native or ADM capsules.

There was no difference in the severity of inflammation between the native capsule (mean score 1 ± 0.28 (SEM)) and ADM capsule (1 ± 0.21 (SEM)), p=1. The location of the inflammation present was different between the two groups. In 87.5% of the native capsules the inflammation was present in the inner layer and 80% of the ADM capsules in the middle or outer layer (p=0. 02)(Figure 48). There was no difference in the severity of perivascular inflammation between the native capsule (mean score 0.58 ± 0.19 (SEM)) and ADM capsule (0.73 ± 0.27 (SEM)), p=0.34 (Figure 48).

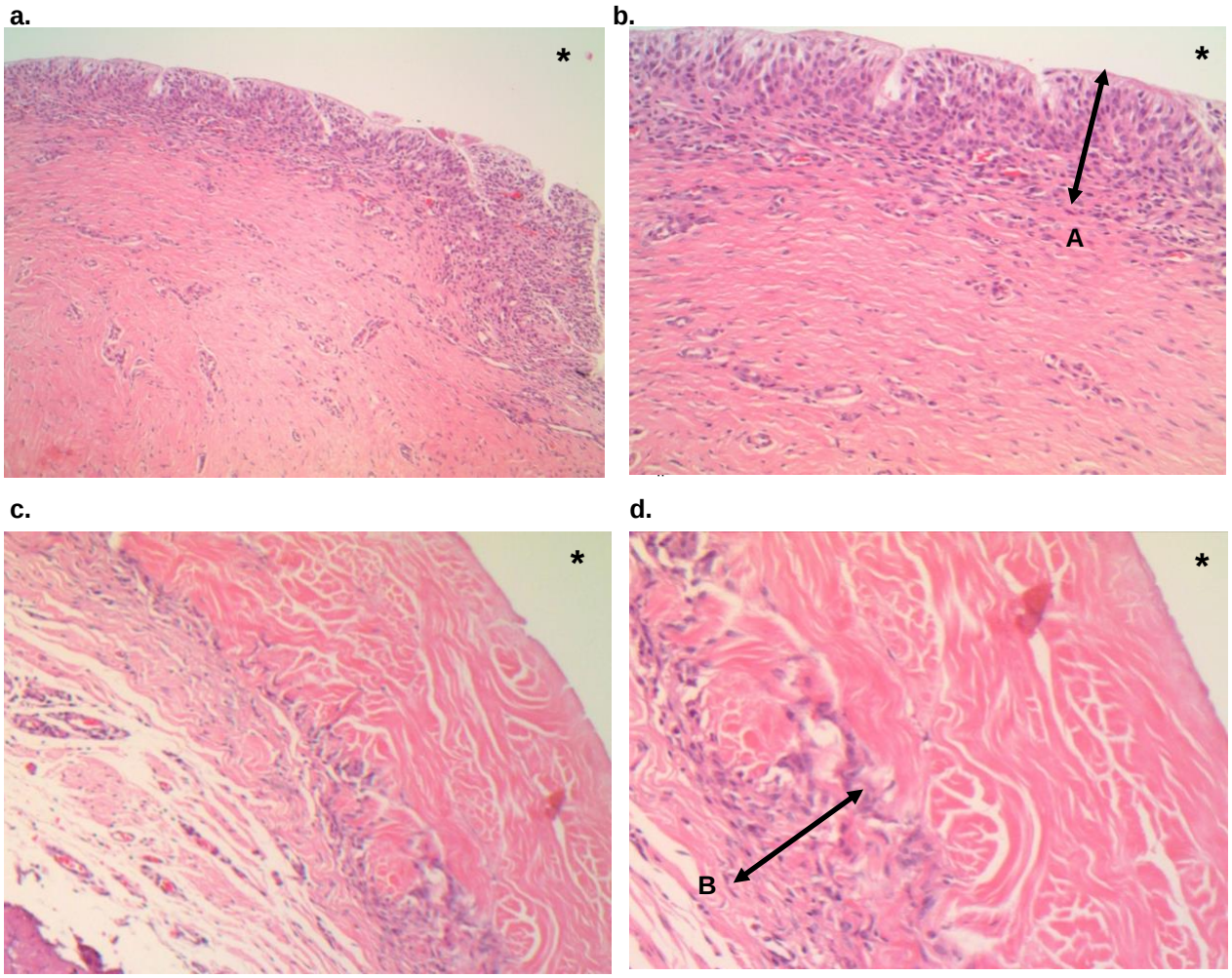


Figure 48 Photomicrographs of H&E staining demonstrating severity and location of inflammation comparing (a) native capsule x100 (b) x200, score 2 for inflammation present in the inner layer (arrow A) with (c) ADM capsule x100 (d) x200, scored 1 for inflammation present in the outer layer (arrow B) (*surface in contact with implant)

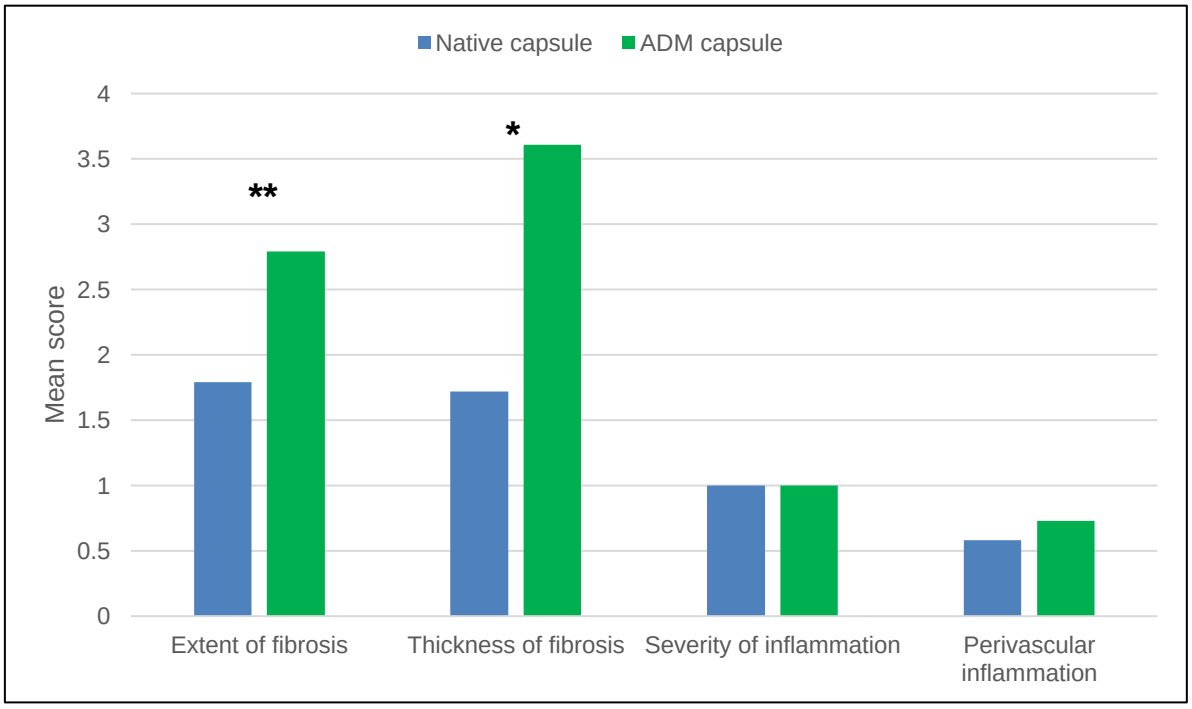


Figure 49 Semi quantitative analysis of native capsule and ADM capsule displaying mean levels of fibrosis and inflammation. There was greater extent of fibrosis ($p<0.001$) and greater thickness of fibrosis ($p=0.02$) in the ADM capsules.
(*$p<0.05$ **$p<0.01$)

Vascularity

Blood vessels were identified as endothelial lined structures containing blood constituents (red blood cells with scattered white blood cells) and manually counted in the two most abundant areas at magnification x20 (0.75mm field diameter). A mean of the two counts was taken per capsule.

There was numerically higher mean blood vessel density in the native capsules (mean count of 38 ± 4 (SEM)) compared to the ADM capsules (mean 23 ± 6 (SEM)), p=0.1 (Figure 50).

a.¶ **b.**

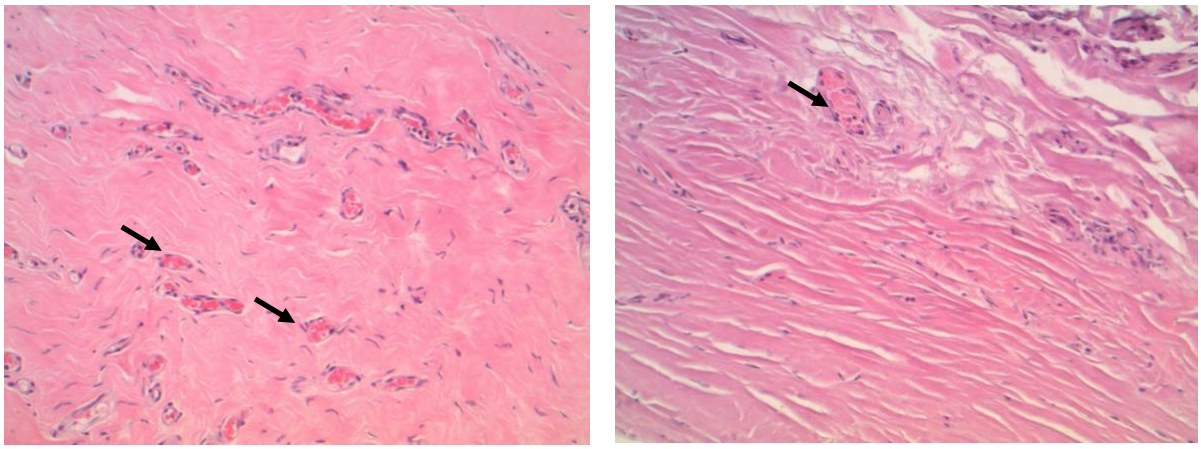


Figure 50 Photomicrographs of H&E staining demonstrating blood vessel density comparing (a) native capsule, count 63 with (b) ADM capsule, count 3 x200. Example blood vessels are demonstrated by black arrows. We found more blood vessels in the native capsule but given the small sample size this did not approach significance.

Cellularity

Fibroblasts were identified by their classical spindle-like, slim, oval, elongated nuclear features and manually counted in the two most abundant areas at magnification x40 (0.50mm field diameter). A mean was taken of the two counts per capsule.

There was no difference in the fibroblast cellularity as assessed using H&E staining between the native and ADM capsules (native capsule mean count 117 fibroblasts ± 9 (SEM), ADM capsule mean count 97 ± 14 (SEM), p=0.26), figure 51.

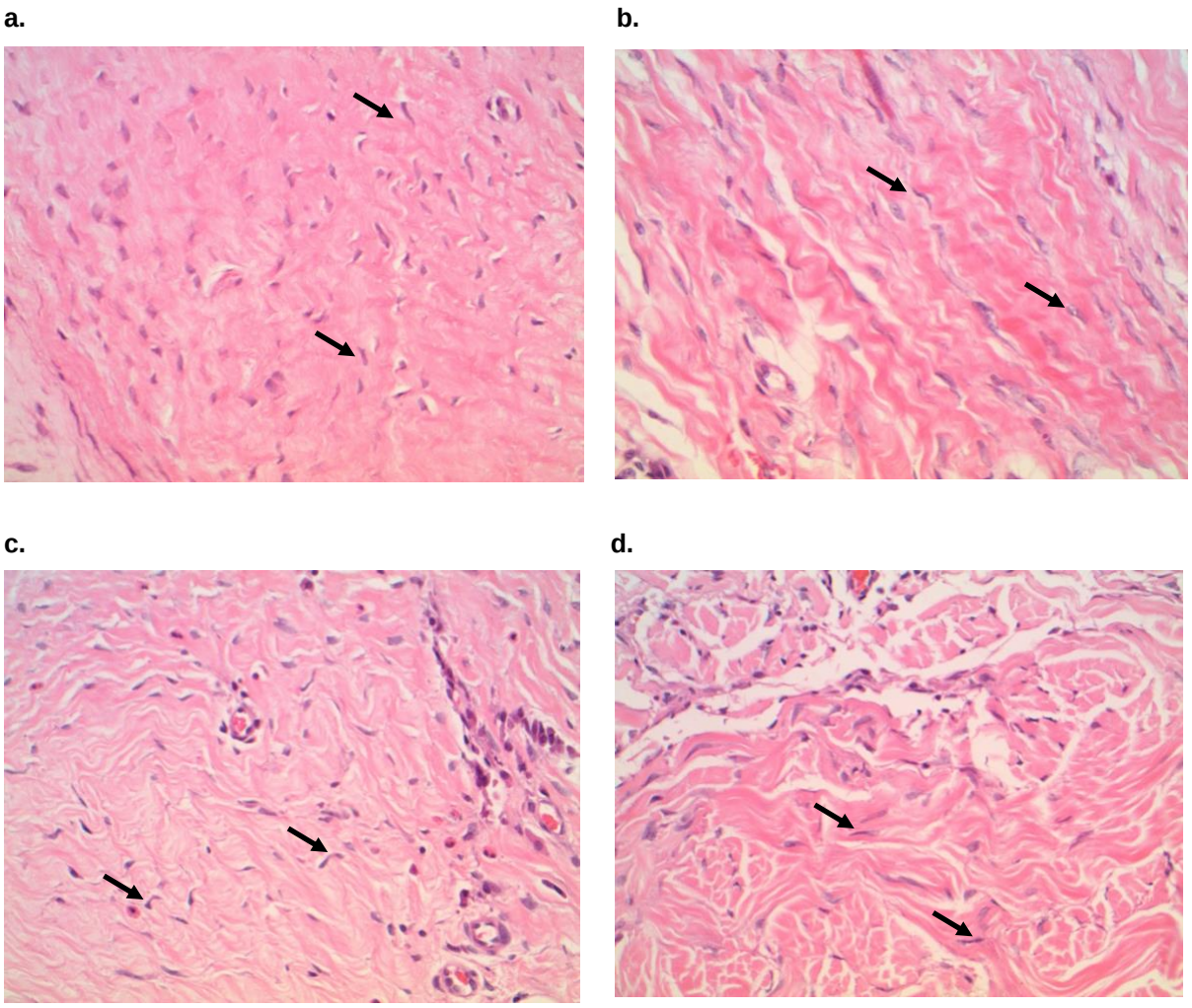


Figure 51 Photomicrographs of H&E staining demonstrating fibroblast cellularity comparing (a) native capsule, count 116 with (b) ADM capsule, count 107, magnification x400 (c) native capsule and (d) ADM capsule, magnification x200. Example fibroblasts are demonstrated by black arrows. We found no difference in fibroblast cellularity between the native capsule and ADM capsule.

Synovial-like metaplasia

A layer of synovial like metaplasia was present in 92% of the native capsules compared to 50% of the ADM capsules, p=0.017. The thickness of this layer was much greater in the native capsules, mean 0.33mm ± 0.07 (SEM) compared to 0.07 ± 0.01 (SEM) in the ADM capsules (Figure 52).

The degree of synovial like metaplasia villous hyperplasia (scored on a scale of 1=mild to 3=severe) was greater in the native capsules (mean score of 1.7 ± 0.25 (SEM) in the native capsules and 1 ± 0.15 in the ADM capsules, p=0.002).

a. **b.**

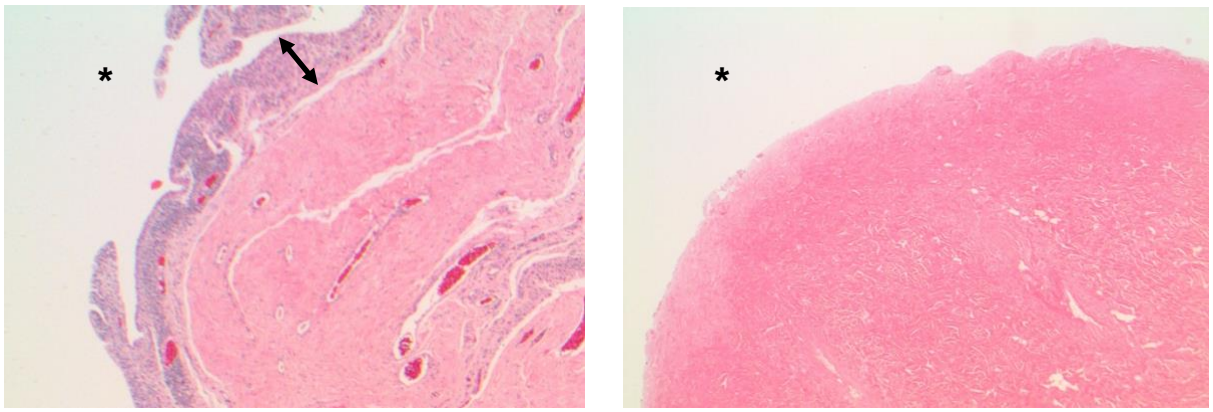


Figure 52 Photomicrographs of H&E staining demonstrating presence of synovial like hyperplasia in (a) native capsule, demonstrated by black arrow and (b) absence of the synovial like hyperplasia layer in the ADM capsule x40 magnification (*surface in contact with implant)

4.3.2 Herovici staining to compare ratio of mature (collagen I) to immature (collagen III) collagen

The herovici stain was analysed using Definiens Tissue Studio®, an automated system which is pre-trained to detect the percentage of red stain (collagen I) and blue stain (collagen III) within the specimen.

There was a higher ratio of mature to immature collagen in the ADM capsule (native capsule mean 1.06 ± 0.33 (SEM) and ADM capsule mean 4.34 ± 1.55 (SEM), p=0.09) (Figure 53).

When subgroup analysis was performed on capsules <2 years in age (n=7) the ADM capsules had a higher ratio of mature to immature collagen than the native capsule (native capsule mean 0.5 ± 0.17 (SEM) and ADM capsule mean 4.05 ± 2.0 (SEM), p=0.14). The only ADM capsule which had a higher proportion of immature collagen was biopsied at 5 months.

In capsules >2 years in age (n=5), again the ADM capsules had a higher ratio of mature to immature collagen than the native capsule (native capsule mean 1.73 ± 0.58 (SEM) and ADM capsule mean 4.69 ± 2.66 (SEM), p=0.4). The only native capsule which demonstrated a higher proportion of mature collagen was biopsied at 54 months from insertion of the implant.

a. b.

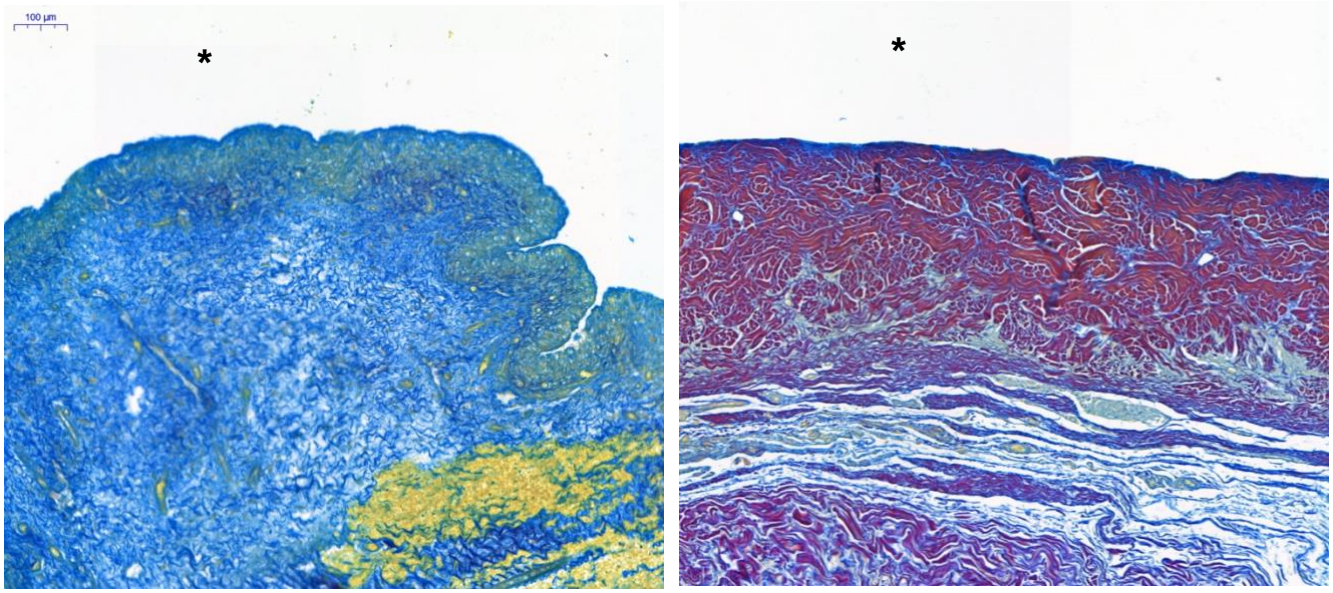


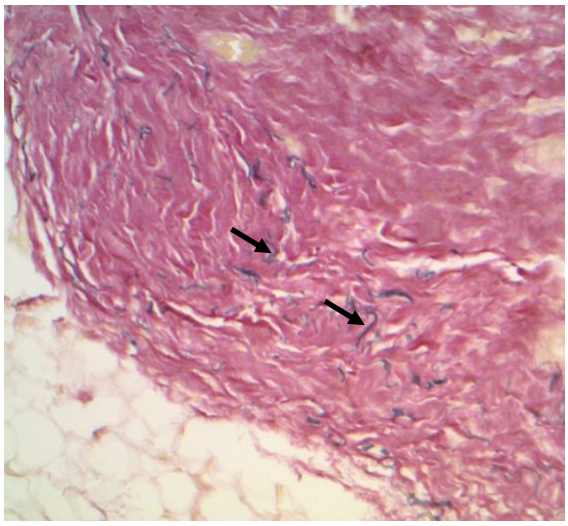
Figure 53 Photomicrographs of Herovici staining comparing (a) native capsule with a ratio of mature to immature collagen of 0.14 and (b) ADM capsule with a ratio of mature to immature collagen of 10.21 at six months of age. The red stain demonstrates the mature collagen I, the blue stain represents the immature collagen III and yellow stain represents cytoplasm. Magnification x10 (*surface in contact with implant)

4.3.3 Elastin Van Gieson staining

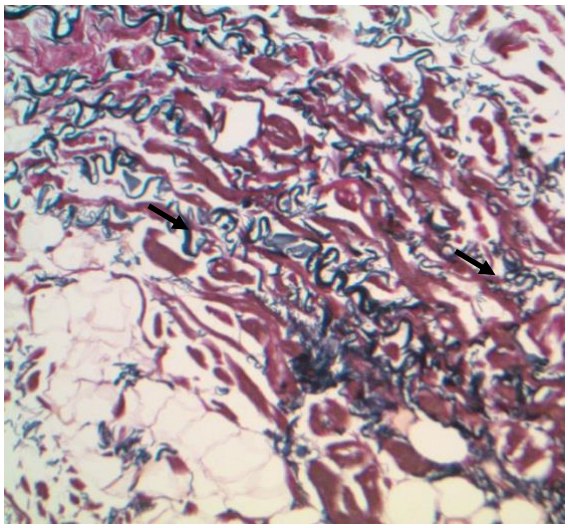
Elastin was semi quantitatively analysed using a score of 0 (none), 1 (occasional elastin fibres with non-elastin stroma between the elastin fibres), 2 (scattered elastin fibres with non-elastin stroma between the elastin fibres), 3 (increased amounts of elastin fibres with occasional areas of densely packed elastin fibres but moderate areas of non-elastin stroma between the elastin fibres), 4 (densely packed elastin fibres with little non-elastin fibres between the elastin fibres).

Overall, there was no difference in the amount of elastin between the native capsules (mean 2.42 ± 0.29 (SEM)) and ADM capsules (mean 2 ± 0.42 (SEM)), p=0.49. The elastin was present in the deep layer in all specimens. When subgroup analysis was performed on capsules <2 years in age (n=7) and capsules >2 years in age (n=5), there was a possible trend for increased elastin in the younger ADM capsules (mean 2 ± 0.38 (SEM) native capsules and mean 2.8 ± 0.58 (SEM) in ADM capsules, p=0.14). In the older capsules, there was a higher proportion of elastin in the native capsule, mean score of 3 ± 0.32 (SEM) compared to a mean of 1.2 ± 0.38 (SEM) in the ADM capsules, p=0.009 (Figure 54).

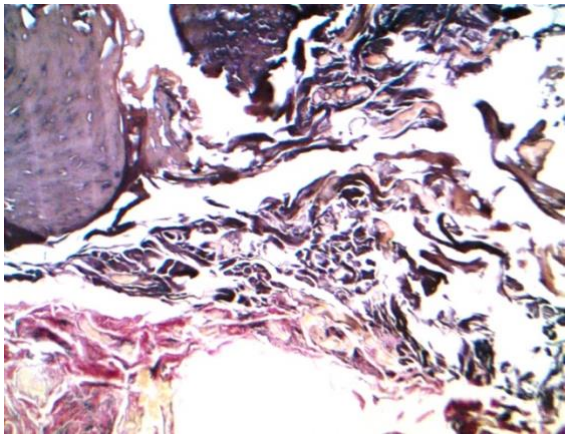
a.¶



b.



c.



d.

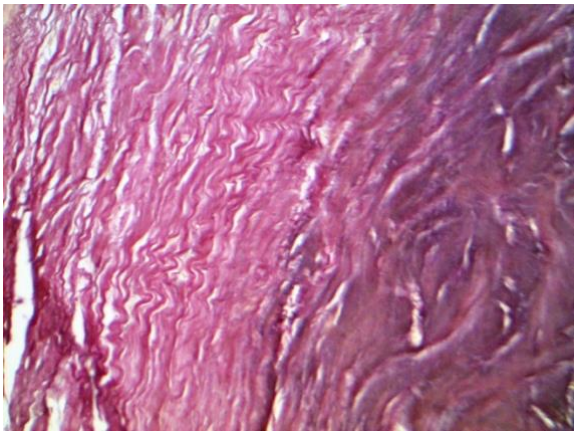


Figure 54 Photomicrographs of Elastin Van Geison staining for elastin comparing (a) native capsule, scored 2 with (b) ADM capsule, scored 4, <2 years in age, demonstrating increased elastin in the ADM capsule, magnification x200 and (c) native capsule, scored 4 with (d) ADM capsule, scored 1, >2 years in age, demonstrating decreased elastin in the ADM capsules, magnification x200. Elastin fibres demonstrated by black arrows

4.4 Comparison of native capsule with ADM capsule using immunohistochemistry

4.4.1 Collagen I and collagen III staining

Collagen I, identified using rabbit anti-collagen I antibody and collagen III, identified using mouse anti-collagen III antibody, was semi-quantitatively analysed using a combined score of intensity of the stain (0 (none), 1 (weak), 2 (moderate), 3 (strong)) and distribution of the stain (0 (none), 1 (patchy), 2 (diffuse)).

There was no difference in the score for Collagen I when comparing the native capsule (mean 2.58 ± 0.22 (SEM)) to ADM capsule (mean 2.86 ± 0.19 (SEM)), p=0.51, (Figure 55). When subgroup analysis was performed on capsules <2 years in age (n=7), no difference was found between the native (mean 2.83 ± 0.33 (SEM)) or ADM capsule (mean 2.75 ± 0.31 (SEM)), p=0.9).

No difference was found in capsules >2 years in age (n=5), (mean 2.3 ± 0.34 (SEM) native capsule and mean 3 ± 0.22 (SEM) in ADM capsule, p=0.12).

There was no difference in the score for Collagen III when comparing the native capsule (mean 3.33 ± 0.24 (SEM)) to ADM capsule (mean 3.15 ± 0.22 (SEM)), p=0.51. When subgroup analysis was performed on capsules <2 years in age (n=7), no difference was found between the native (mean 3.4 ± 0.37 (SEM)) or ADM capsules (mean 3.3 ± 0.34 (SEM)), p=0.7. No difference was found in capsules >2 years in age (n=5), (mean 3.1 ± 0.46 (SEM) native capsules and mean 3 ± 0.32 (SEM) in ADM capsules, p=0.62).

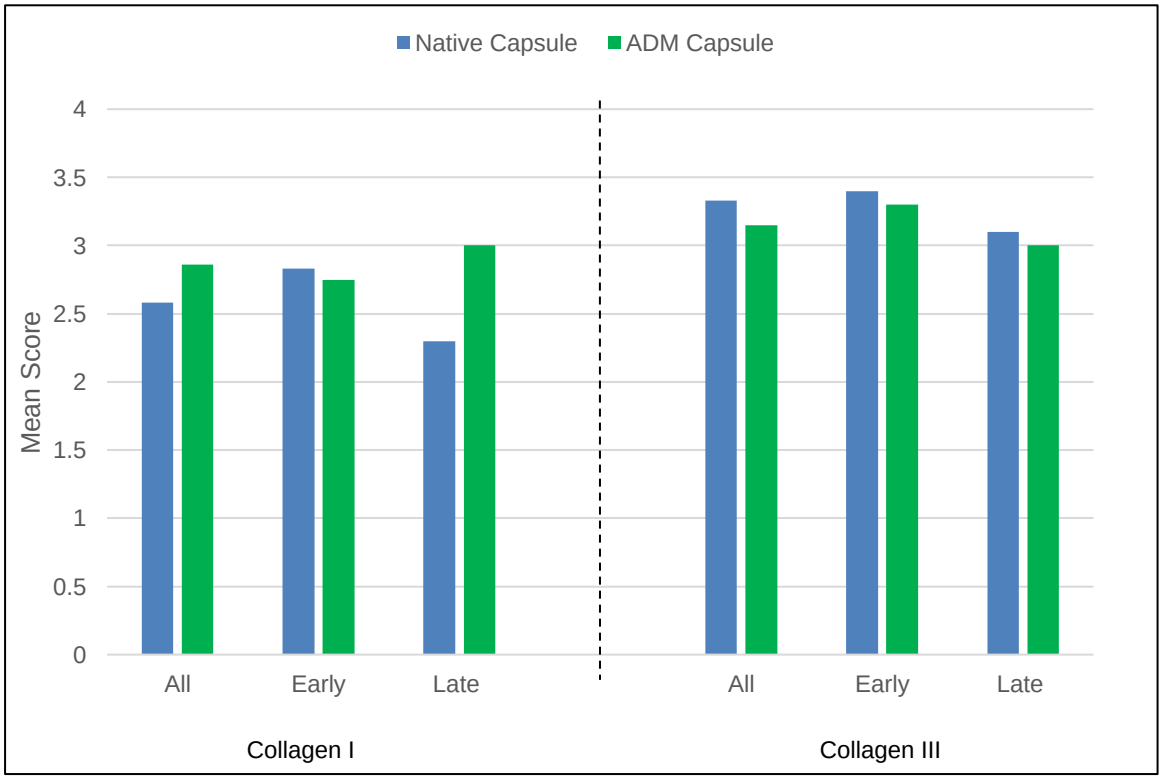


Figure 55 Semiquantitative analysis of collagen I and III stain comparing native capsule and ADM capsule at all time points from implant insertion, early (<2 years) and late (≥2 years). All scored from 0 - 5 (intensity (0 (none) to 3 (strong)) + distribution (0 (none) to 2 (diffuse)). No differences were demonstrated.

4.4.2 Alpha smooth muscle actin (a-SMA) stain for myofibroblasts

Myofibroblasts were detected using mouse anti—smooth muscle actin antibody. From each specimen, a mean was taken of the percentage of positively stained fibroblasts in the two most abundant areas, magnification x40 (0.75mm field diameter).

The percentage of myofibroblasts was greater in the ADM capsule (46.7 ± 9.6 (SEM)) compared to the native capsule (22.8 ± 6.3 (SEM)), p=0.04 (Figure 56). When subgroup analysis was performed on capsules <2 years in age (n=7), no difference was found between the native (mean 32.3 ± 8.3 (SEM)) or ADM capsule (mean 50.4 ± 13.0 (SEM)), p=0.19). No difference was found in capsules >2 years in age (n=5), (mean 9.4 ± 6.4 (SEM) native capsule and mean 41.5 ± 15.7 (SEM) in ADM capsule, p=0.15).

When comparing the native capsules alone, the percentage of myofibroblasts in the younger capsules was greater than in the older capsules (mean 32.3 ± 8.3 (SEM) vs. 9.4 ± 6.4 (SEM), p=0.07). There was no difference between the younger (mean 50.4 ± 13.0 (SEM)) and older (mean 41.5 ± 15.7 (SEM)) ADM capsules, p=0.67.

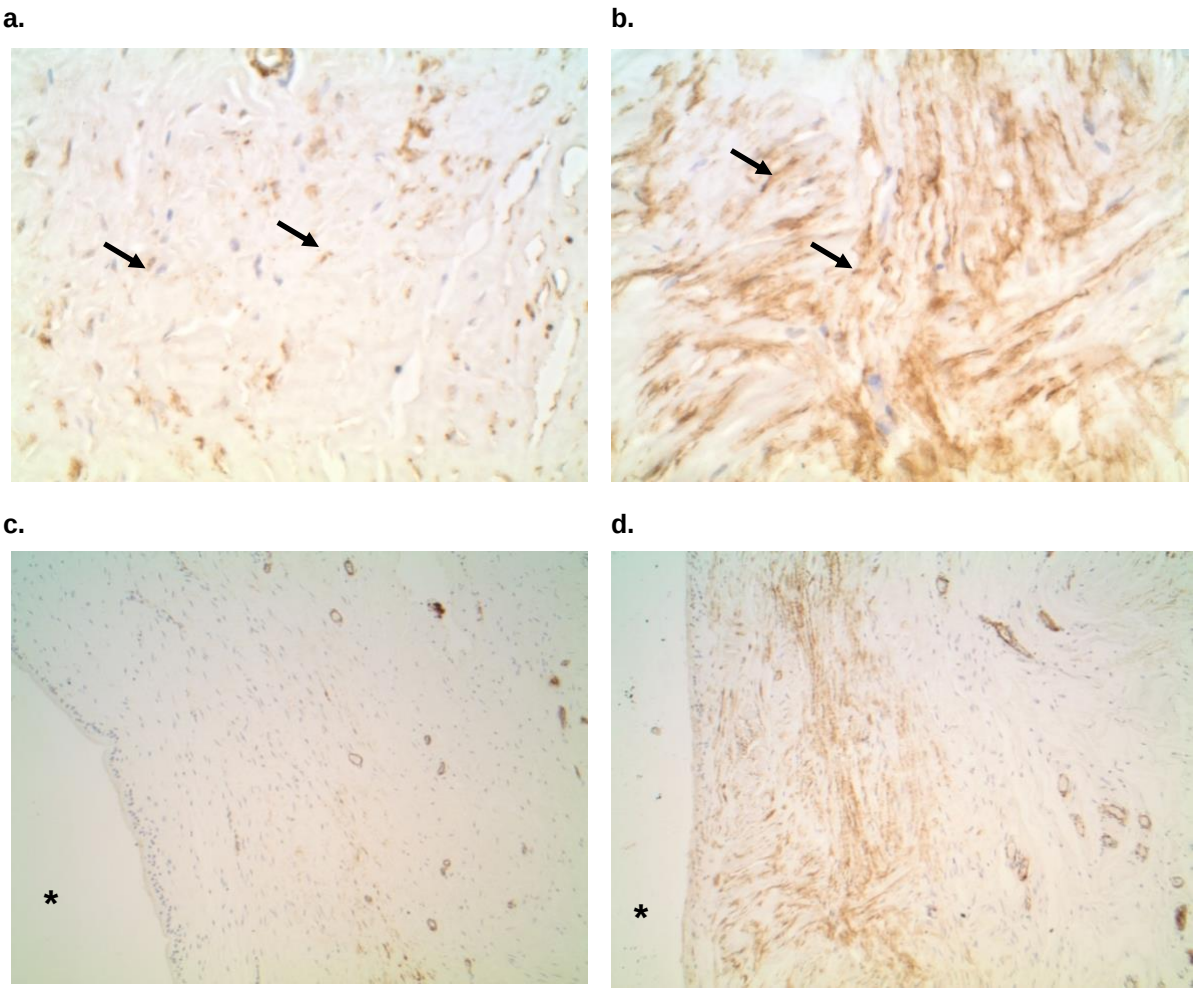


Figure 56 Photomicrographs of a-SMA stain for myofibroblasts comparing (a) native capsule, count 25% and (b) ADM capsule, count 82.5% magnification x400 and (c) native capsule and (d) ADM capsule Magnification x100 Example fibroblasts demonstrated by black arrows (*surface in contact with implant). We found higher percentage of myofibroblast in the ADM capsules.

4.4.3 Fibronectin

Fibronectin, identified using rabbit anti-fibronectin antibody, was semi-quantitatively analysed using a combined score of intensity of the stain (0 (none), 1 (weak), 2 (moderate), 3 (strong)) and distribution of the stain (0 (none), 1 (patchy), 2 (diffuse)). Each layer of the capsule was analysed then a total score given.

Fibronectin was present predominantly in the inner and middle layer of the capsule in both the native and ADM capsule. There was no difference between the total scores of the native capsule (mean 6.4 ± 0.43 (SEM) and ADM capsule (mean 6.25 ± 0.73 (SEM), p=0.12 (Figure 58). There was no difference in the inner (native capsule, mean 3.01 ± 0.08 (SEM) and ADM capsule, mean 2.75 ± 0.25 (SEM), p=0.33), middle (native capsule mean, 2.33 ± 0.19 (SEM) and ADM capsule, mean 2.36 ± 0.31 (SEM), p=0.78) or outer (native capsule mean, 1 ± 0.3 (SEM) and ADM capsule mean, 1 ± 0.33 (SEM), p=0.84) layer of the capsule (Figure 57).

When subgroup analysis was performed on capsules <2 years in age (n=7) and capsules >2 years in age (n=5), there was no observed difference between the native and ADM capsules.

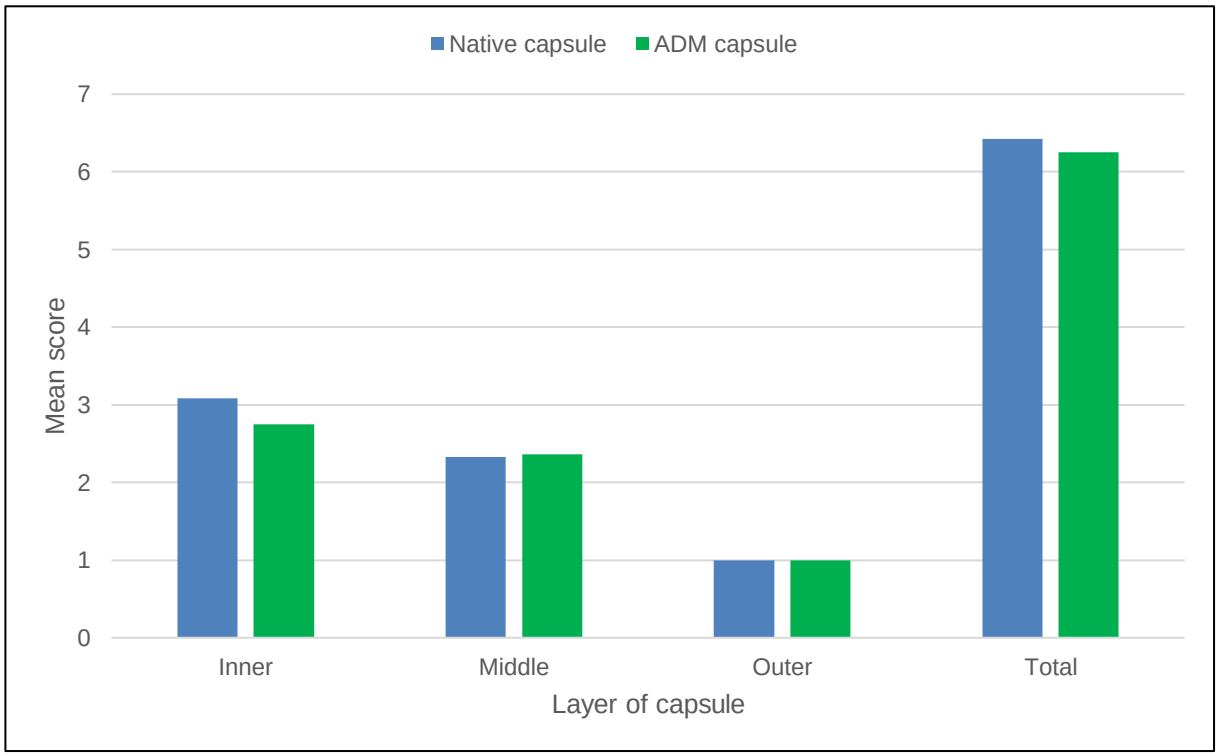


Figure 57 Semi quantitative analysis of fibronectin comparing native capsule and ADM capsule in total and within the three layers of the capsule. Each layer scored from 0 - 5 (intensity (0 (none) to 3 (strong)) + distribution (0 (none) to 2 (diffuse)) and a total given. No differences were demonstrated between the native and ADM capsule but the fibronectin was most abundant in the inner and middle layers of both capsules.

a. **b.**

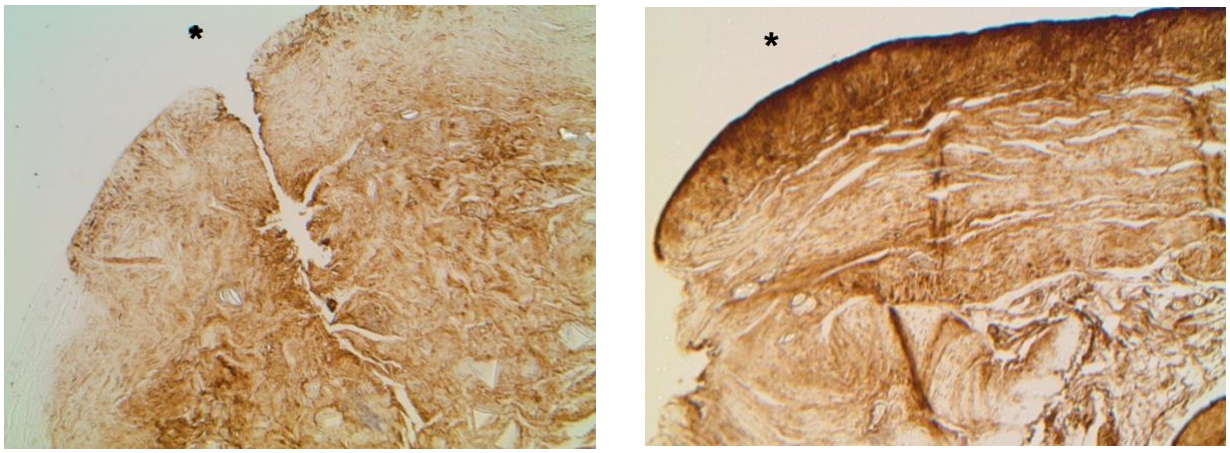


Figure 58 Photomicrographs of fibronectin stain comparing (a) native capsule, scored 5 and (b) ADM capsule, scored 6, magnification x100 (*surface in contact with implant). Demonstrating no difference in quantity of fibronectin between the native and ADM capsule and most abundant in the inner and middle layers of both capsules.

4.6 Discussion

This study has compared the breast implant capsule deep to pectoralis (native capsule) and for the first time deep to a porcine ADM (ADM capsule) to illicit differences in key markers of inflammation and fibrosis in order to improve our understanding of how ADM affects capsule formation in implant based breast reconstruction.

There was no difference in the severity of inflammation between native and ADM capsules in our study, unlike two previous studies which showed less inflammation in ADM capsules compared to native. However, in these studies the ADM was human, unlike our porcine ADM (243, 245). This may be secondary to the difference in composition of human and xenogenic ADMs along with their different processing and sterilization techniques. Although the products are marketed as an acellular scaffold for the host tissues to incorporate in to, and the aim of the manufacturing process is to remove antigenic epitopes which may incite an inflammatory response, SurgiMend is still identifiable as bovine tissue immunohistochemically (215). Other studies have demonstrated the presence of nucleated cells within the matrix and in-vitro differences in cytocompatibility where certain ADMs more readily support cell growth (290, 291). Both the previous human ADM studies assessed the capsule at an earlier time frame (mean 4.4 months, maximum 10 months and mean 5.6 months, maximum 13 months respectively) compared to this study which measured at a longer mean time of 27.8 months (maximum 81.5 months) (243, 245). Given capsular contracture occurs over time it may be that the ADM slows down capsular contracture as oppose to completely prevents it.

Inflammation was present in the middle and outer layers of the capsule in the ADM group compared to the inner layer in the native group, suggesting that the foreign body reaction is occurring at the skin flap and ADM interface as oppose to the implant ADM interface. This finding would support the theory ADMs reduce capsular contracture by acting as a barrier between the native tissues and implant.

Although other studies have found reduced fibroblast cellularity in the ADM capsule (243), our current study shows no difference. This may be again due to the earlier time points of 4.4 months (mean) at which the biopsies were taken compared to 27.8 months in this study. Increased cellular infiltration is also seen as part of integration of the ADM (201) therefore the difference seen in this study may be representative of integration as oppose to an increase in the foreign body reaction.

Angiogenesis is also a sign of host tissue regeneration and integration of the ADM (201). This is likely to account for the little difference seen in vascularity between the two capsules at a longer mean time of 27.8 months from implant and ADM insertion in this study, compared to a decreased vascularity in the ADM group in other studies with a shorter mean time of 4.4months (243, 244) and 5.6 months (292) from implant and ADM insertion.

Characteristically capsules have three layers; the inner highly cellular synovial like metaplasia layer, middle highly cellular within loosely arranged connective tissue layer and outer dense connective tissue rich in collagen fibres layer. Within the ADM capsules, 50% did not have the inner layer which corresponds with analysis from capsules of SurgiMend (foetal bovine dermis) assisted reconstructions (215). This suggests a reduced foreign body response at the ADM-implant interface compared to the native tissue-implant interface. Further supporting this theory, in the 50% where an inner layer was present there was a significantly lower degree of synovial like metaplasia villous hyperplasia in the ADM capsule. This layer was thinner in the ADM capsule, 0.07mm compared to 0.33mm in the native capsule, although there is no evidence to suggest correlation between thickness of the capsule and degree of contracture. This inner synovial like metaplasia layer disappears with time in breast capsules (103). Synovial like metaplasia has also been found in other healing skin and soft tissues suggesting it is a component of the earlier phases of wound healing. The foreign body reaction may be at a later phase in the ADM capsules than the native capsules which is why it is not present in over 50%. Or the reduced vascularity in this area may lead to a less intensive response. Movement is an important factor in the formation of synovial metaplasia (293). Breast implants are not static within the created pocket. However, there may be reduced movement in the lower pole fixed with ADM compared to the upper pole covered by pectoralis muscle, hence reduced synovial like metaplasia in the ADM capsules. There is the possibility that this layer was never present in the ADM capsule however without serial testing of the same capsules it is impossible to know.

The foreign body reaction consists of a number of stages starting from the first minutes after the initial insult continuing potentially for the lifetime of the inserted device, whether in an active or dormant state. During the granulation phase the tissue formed is largely composed of collagen III (immature collagen). Over the following weeks to months the granulation tissue is degraded and remodelled to form the final fibrotic capsule. Collagen I (mature collagen) is the predominant composite of this fibrotic capsule. This study demonstrated younger ADM capsules (less than two years) may have a greater proportion of mature collagen than younger native capsules which may suggest that the foreign body reaction is occurring in the ADM capsules over a shorter time period and is not actually delayed, which has previously been hypothesised. It is potentially occurring over a shorter duration and ends forming a mature ‘final’ capsule. The only native capsules demonstrating a greater proportion of mature collagen were biopsied almost five years from implantation suggesting at the native tissue implant interface the foreign body reaction is more intense and over a longer duration. Although investigating biofilms on subpectoral capsules, ADM capsules and implant shells, Poppler et al. also demonstrated a stable higher mean ratio of collagen I to III in the ADM capsules in both younger and older capsules (112). On clinical assessment, using Baker grade, there were no differences between the capsules of varying ages from six months to five years, suggesting that there is no further ongoing reaction at the ADM – implant interface and the foreign body reaction remains dormant, hence the reduction in capsular contracture. Further long-term clinical follow-up of the cohort and assessment of larger numbers would strengthen this conclusion.

We report elastin in the outer layer of the capsule in native and ADM capsules, consistent with a previous study of non-contracted capsules (248). This contrasts with a study of contracted capsules, where elastin was seen in the inner layer of the capsule (135). However, in our study, only two reconstructions had grade II capsules. We found no significant difference in elastin content between the native and ADM capsules but slightly increased elastin content in the ADM capsules less than 2 years in age, similar to other published data (248). A higher elastin content in the native capsules greater than two years in age may again support the theory that the foreign body reaction is still ongoing and has not reached the later phase of a 'matured wound' that the ADM capsules have reached. In skin and scarring as a wound heals and collagen increases, elastin decreases (98).

The percentage of myofibroblasts was significantly higher in the ADM capsules which differs to that published in the literature, where either decreased numbers (244, 245) or no difference in numbers (248) was found when comparing human ADM and native capsules. This study is the first to quantify myofibroblasts in porcine ADM which may account for the differences seen, as previously discussed, the differences in composition and manufacturing techniques can affect the native tissue response.
During the later phases of wound healing the ratio of myofibroblasts to fibroblasts initially increases before reducing by apoptosis (294). The ADM capsules have a higher percentage of myofibroblasts suggesting they have reached this later phase. In breast augmentation capsules the average time from implantation to finding a capsule negative for myofibroblasts is 5 years (106). During the earlier granulation phase of the foreign body reaction there are very few myofibroblasts present (89) and composition is largely collagen III. Our findings would suggest the native capsules have reached this phase, again proposing the foreign body reaction occurs over a longer duration at the implant-native tissue interface. When ADMs are inserted into the body they become recolonized with fibroblasts and myofibroblasts, along with other cells (201). Increased cellular infiltration has been found to correlate with a greater degree of ADM remodelling (290) which could also account for an increase in myofibroblasts within the ADM capsule. Although hypothesized that myofibroblasts play a role in capsular contracture, myofibroblast numbers are not shown to correlate with grades of capsular contracture (106). In ADMs, myofibroblasts may have a physiological but not pathological role. These results support findings in a mouse model comparing capsules of implants wrapped in Strattice™ where a rich myofibroblast layer initially increased until 12 weeks then steadily decreased to baseline levels (3 weeks) by 52 weeks (242, 295). The biopsy however gives a snap shot of one time point only and other factors could at that point have caused an increase in myofibroblasts which has no clinical significance.

Fibronectin, an adhesive protein with a significant role in cell adhesion, growth, migration and differentiation (296) has previously been found in the inner capsule layer (101). In this current study, fibronectin was predominantly found in the inner and middle layers of both native and ADM capsule. There was no difference between the presence of fibronectin within ADM compared to native capsules.

Fibronectin binds to type III collagen rather than other types (297) however no differences were observed in the capsules with a higher collagen III ratio. Dysregulation of fibronectin is associated with fibrosis therefore differences maybe be observed in contracted breast capsules.

The native capsules and ADM capsules were matched as both sets of biopsies were taken from the same patient, reducing confounding factors. All of the implants were textured except for one polyurethane therefore it is impossible to make any assumptions on difference between implant surface. The only notable difference was a higher fibroblast count in the polyurethane capsule which was greater than 2 years in age compared to the textured capsules also greater than two years in age. In animal models polyurethane coated implants have been associated with a more intense foreign body reaction and myofibroblasts presence (190, 191) but there is no published literature comparing capsules in ADM reconstruction with polyurethane implants. Two of the bilateral cases had a post-operative haematoma in one breast requiring evacuation, no differences were seen in either the ADM or native capsules between each breast in these two participants to suggest the presence of a haematoma may influence the capsule.

The main weaknesses of this study are the small sample size and the single time point of the biopsies, although this study has a much longer time range from implantation than other published work. The gold standard design would be serial sampling of the same capsules however this is not clinically or ethically possible. We used a semi-quantitative scoring system to analyse the stains by a blinded pathologist with over 20 years of experience in breast pathology which was further validated by another pathologist with over 85% agreement. We considered the automated image-analysis system such as Definiens Tissue Studio® not to be standard practice and with the possibility of false results due to artefactual staining being inappropriately analysed and user errors we deemed a highly experienced histopathologist to be more reliable.

The availability of contracted capsules within the study sample would have given the opportunity to draw further conclusions on how ADM may prevent capsular contracture in implant based breast reconstruction.

In summary, compared to native capsules, ADM capsules demonstrated:

- a thicker more extensive middle/outer fibrotic layer
- reduced inner, synovial like metaplasia layer
- A higher ratio of collagen I (mature) to collagen III (immature)
- Greater percentage of myofibroblasts
- Less elastin in capsules greater than 2 years in age

This study provides preliminary evidence to suggest ADMs may reduce capsular contracture by creating a barrier between the native tissues and implant, leading to a shorter, less intense foreign body response which remains dormant over time. Any results from this study should be interpreted with caution given the small sample size and would require revalidation in a follow-up study.

5. Conclusions

5.1 Conclusions

The BROWSE study has demonstrated equivalent implant loss in Strattice™-assisted and submuscular implant based breast reconstruction despite an increase in treatment for post-operative infection and wound dehiscence. The change in practice to a more aggressive approach in the management of post-operative complications with an increase in return to theatre rate is likely to account for these findings. Through an unbiased clinical assessment of both Strattice™-assisted and submuscular reconstructions we demonstrated a trend towards a lower rate of capsular contracture in Strattice™-assisted reconstructions, although not as low as expected. Further supporting these findings in the larger cohort, was a significantly lower rate of revision surgery for capsular contracture in the Strattice™-assisted reconstructions. Improved aesthetic outcomes were exhibited in the Strattice™-assisted reconstructions as assessed by a blinded breast surgeon, breast care nurse and lay person. Despite the positive findings in Strattice™-assisted reconstructions there were no differences elicited in patient reported outcomes between Strattice™–assisted and submuscular reconstructions.

The Capsule study has demonstrated both short and long-term differences in capsule composition between native and porcine ADM capsules based on histology and immunohistochemistry techniques. The findings in the ADM capsules of, a thicker more extensive middle/outer fibrotic layer, reduced inner, synovial like metaplasia layer, a higher ratio of collagen I (mature) to collagen III (immature), a greater percentage of myofibroblasts and less elastin in capsules greater than 2 years in age suggest ADMs may reduce capsular contracture by creating a barrier between the native tissues and implant, leading to a shorter, less intense foreign body response which remains dormant over time.

In conclusion, the findings described in this thesis have provided much needed long-term outcome data to substantiate the benefits of reduced capsular contracture and improved aesthetic outcomes in ADM-assisted reconstruction. This, together with preliminary scientific evidence of how ADMs impact constituents of the foreign body response suggest ADMs may play a successful role in the prevention and management of capsular contracture.

5.2 Limitations of the work

The main limitations of the BROWSE Study are the retrospective data collection of complication data and large differences in numbers of submuscular reconstructions performed across the three centres which may have skewed the data. Ideally all patients should have completed a pre-reconstruction BREAST-Q to allow the post-operative data to be analysed against baseline scores.
This study only considered the outcomes with the use of Strattice™, a porcine dermis however many other ADM products are available on the UK market and are being used in clinical practice without

any long-term data but evidence of short-term success. It is difficult to know whether the results of this study will be applicable to other ADMs.
Since embarking on this research surgical practice has evolved with many different techniques being introduced and popularised; including pre-pectoral reconstruction and ADM and dermal sling reconstructions which prevent lifting the pectoralis muscles at all. The number of pre-pectoral reconstructions in this cohort was very small (<5%) and from one centre therefore no meaningful data could be extrapolated.

The main limitation to the Capsule Study is the small sample size, especially of capsules of more than two years since insertion of the implant (n=5). Although the aetiology of capsular contracture remains uncertain we do know it increases with time in both augmentation and reconstruction without ADM use (46) therefore the older the capsule the more differences we may have elicited between native and ADM capsules. The differences demonstrated should also be validated with gene and protein analysis although this was beyond the scope of the available resources for this project. It would also be beneficial to compare native and ADM capsules of contracted capsules (Baker III/IV) but during the recruitment period of this study no cases were available.

5.3 Recommendations for future work

This study has provided the most robust UK evidence of long-term outcomes in sub-pectoral Strattice™-assisted reconstructions compared to a submuscular technique however there has now been evolvement of surgical techniques towards pre-pectoral ADM reconstructions or pre-pectoral ADM/dermal sling reconstruction. The pre-bra study is underway to establish the safety and effectiveness up to 18 months of pre-pectoral reconstruction (298). Therefore, future work should include a study of long-term outcomes using these techniques. The most robust way would be to perform a randomised control trial however given the huge popularity of such techniques I believe it would be very difficult to recruit to from both a surgeon and patient perspective and a prospective cohort study design would be more successful.

The Capsule study provided preliminary scientific evidence of how ADMs may reduce capsular contracture in breast reconstruction using histology and immunohistochemistry techniques. These findings need to be further validated with gene and protein analysis. Further work should also include RNA sequencing to identify new dysregulations which may account for the differences in clinical outcome. This work should be performed on older and contracted native and ADM breast capsules also.

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7. Appendices

7.1 Participant invitation letter

University Hospital of South Manchester NHS
NHS Foundation Trust

Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
M23 9LT
Tel: 0161 998 7070

Date [insert date]

Dear [Insert name]

We would like to invite you to take part in a Research Study looking at the outcomes of Breast Reconstruction surgery. The research study will involve a single visit to [insert name of hospital] for clinical assessment and we will ask you to tell us how you feel about your reconstruction in a questionnaire. This study will help inform other women on what to expect from their reconstruction.

Study title: Breast Reconstruction Outcomes with and Without Strattice (BROWSE)
Principal Investigator: Mr. Richard Johnson

We would be grateful if you could take the time to read the enclosed Information Sheet about the study which lets you know what is involved in the study.

If you could let us know your interest by completing the slip below and returning it to us in the Self Addressed Envelope enclosed please. If you agree to be approached about the study one of our researchers will contact you to answer any questions. If you are not interested in taking part we will not attempt to contact you again.

✂----------✂----------✂

Name: [insert name]
I am/ am not (*delete as applicable) potentially interested in taking part in the above research study.

7.2 BROWSE participant information sheet

University Hospital of South Manchester NHS
NHS Foundation Trust

Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
M23 9LT
Tel: 0161 998 7070

Sponsor: LifeCell EMEA Limited

Oxford, United Kingdom

Study title: Breast Reconstruction Outcomes with and Without StratticE (BROWSE)

Principal Investigator: Mr. Richard Johnson

Name of Organization: University Hospital of South Manchester

You are being invited to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it will involve. Please take time to read this information sheet carefully and discuss it with friends, relatives and your GP if you wish. Please ask us if anything is not clear or if you would like more information.

Introduction

Breast reconstruction using implants has been done for many years. Sometimes breast reconstructions use a material called Strattice™ Reconstructive Tissue Matrix to help support the implant. We do not know what the long-term benefits of Strattice™ may be to women having this type of reconstruction. This study will look at whether there are any long-term benefits of using Strattice™ for implant based breast reconstruction compared to women in whom this product was not used.

What is the idea behind this study?

Breast reconstruction with an artificial breast implant is an accepted method of reconstruction after mastectomy. However, over time the reconstruction tends to change. In this study we want to look at the how these reconstruction fare over time. We are interested in how women feel about their reconstructions, how soft the reconstruction are and whether the implants harden (form capsular contracture) over time.

What is the purpose of this study?

This study is to see if breast reconstructions using Strattice™ Tissue Matrix are better or worse than reconstructions without Strattice™ Tissue Matrix.

Why am I being invited to take part?

You have had an implant based reconstruction in the recent past. We would like find out how you feel about the reconstruction and how well the shape of the reconstruction has done with time. This study is being performed in three hospitals in the UK. If you agree to take part you will need to come back to the hospital for one clinic visit to assess your breast reconstruction and you will be asked to fill out a questionnaire on how you feel about your reconstruction. The questionnaire will be sent to you again, one year later for comparison.

Do I have to take part?

It is up to you to decide whether or not to take part. If you agree to join you are still able to leave the study at any time without giving a reason. If you leave the study it will not affect the standard of care you receive.

What product is being investigated or used and what does it do?

This study involves looking at the use of Strattice™ Tissue Matrix which is a surgical mesh that is made of pig skin. It is used in surgery to help to hold the implant in your breast in place. Some women in the study will have had this used in their breast operation and some have not.

What will be done if I take part in this study?

If you take part in this study, you will be asked to visit your hospital for one check-up after your surgery. You will be seen by a female Breast Surgeon in the clinic who will ask to examine you and to use a gentle pressure device. You will be asked to complete a questionnaire about how you feel about your reconstruction and then a final questionnaire a year later to see if things have changed with time.

Do I have to have medical photographs taken?

You will be asked as part of the study if you would be willing to have photographs taken of your breast reconstruction(s). The photographs will not include your face. If you do not wish to have medical photographs taken you can still take part in the other parts of the study.

How could taking part in this study help me?

There is no direct benefit to you of taking part in the study, the study will help to inform women in the future of what to expect from their breast reconstructions. Although Strattice™ Tissue Matrix has been used in breast reconstruction since 2008; there are no large long-term studies on how it compares to traditional reconstruction with an implant. Taking part in this study may help other women, in the future, to make decisions about their choice of reconstruction. It may also help us find out whether using Strattice™ Tissue Matrix is a good use of money for the NHS.

Will I have to pay anything to be in the study?

No. But as you will have to travel to the hospital to be assessed, you will receive a gift voucher for £45.

Who is organising and funding the research?

The BROWSE Study is organised by breast surgeons at the University Hospital of South Manchester, together with researchers at LifeCell EMEA Ltd (the company that makes Strattice™ Tissue Matrix). Your doctor will not receive any personal financial payment if you take part.

Who will see my medical notes?

Your surgeon, nurse and the hospital study staff will know you are taking part in the study, and have access to your medical notes. Your GP will be told that you are involved in the study, if you decide to take part.

What if I don't want to carry on with the study?

If you change your mind about taking part in the study you are free to withdraw at any time. This will not affect your future clinical care in any way.

Who reviewed this study?

The BROWSE study has been approved by the Research Ethics Committee on behalf of all hospitals throughout the UK. It has also been reviewed and approved by the National Institute for Health Research.

Who can I contact if I have any questions?

If you have any questions you may ask them at any time, even after the study has started. If you wish to ask questions later, you may contact:

Mr. Richard Johnson at The Nightingale Breast Unit, Wythenshawe Hospital on 0161 998 7070 and ask to be put through to the Nightingale Unit reception.

If you would like to discuss the study with someone who is not involved in the study, please contact your local Patient Advice and Liaison Service (PALS) at pls@uhsm.nhs.uk or telephone 0160 291 5600.

7.3 BROWSE CRF

University Hospital of South Manchester NHS
NHS Foundation Trust

CASE REPORT FORM

Breast **R**econstruction **O**utcomes **W**ith and without **S**trattic**E**

Clinical Trial Site Name: UHSM/RVI/BRI

Chief Investigator: Mr. R. Johnson

Co-investigators: Miss. C. Kirwan, Mr J. Harvey,

Ms R. Wilson, Mr J. O'Donoghue and Mr. R. Linforth

Participant Initials: _____

Participant Study Number:

STUDY: BROWSE

Baseline Visit 1

Date of visit: **Centre:**

Screening Inclusion Criteria **ALL ANSWERS SHOULD BE COMPLETED YES**

		Yes	**No**
1	Patient is female >18	☐	☐
2	Patient is capable of informed consent	☐	☐
3	Implant based breast reconstruction with or without Strattice >6 months ago	☐	☐

Screening Exclusion Criteria **ALL ANSWERS SHOULD BE COMPLETED NO**

		Yes	**No**
1	Delayed reconstruction	☐	☐

Confirm eligibility to study: Yes ☐ No ☐

Date of consent: (Version……. Date:……..)

Date notes audited:

According to the patient any further intervention since:

_____

_____

_____

Baseline details:	
Date of birth	☐☐/☐☐/☐☐☐☐
Age at registration	☐☐
Height (m)	☐☐☐
Weight (Kg)	☐☐☐
BMI	☐☐. ☐ kg/m^2

At the time of the initial surgery:

Relevant Past Medical History

Relevant Medications

Diabetes: Yes ☐ No ☐

Smoker: Yes ☐ No ☐ Ex ☐

Previous chest wall radiotherapy Yes ☐ No ☐

CLINICAL DETAILS

Neo-adjuvant treatment: Yes ☐ No ☐

Dates _____

LEFT BREAST

Consultant _____

_____

Date of surgery _____

_____

Reason for surgery:

Risk reducing ☐ Cancer ☐ DCIS ☐

Mastectomy performed:

SSM ☐ NSM ☐ Simple ☐

Reconstructive procedure performed:

Total cover Strattice ☐

Subpectoral + Strattice ☐

Total submuscular coverage ☐

Upper pectoral coverage ☐

Subcutaneous implant ☐

Dermal sling ☐

Other _____

RIGHT BREAST

Consultant

Date of surgery

Reason for surgery:

Risk reducing ☐ Cancer ☐ DCIS ☐

Mastectomy performed:

SSM ☐ NSM ☐ Simple ☐

Reconstructive procedure performed:

Total cover Strattice ☐

Subpectoral + Strattice ☐

Total submuscular coverage ☐

Upper pectoral coverage ☐

Subcutaneous implant ☐

Dermal sling ☐

Other _____

LEFT BREAST

Incision used:

Horizontal ☐

Lateral ☐

Vertical ☐

Wise pattern ☐

IMF ☐

Weight of specimen (g) _____

RIGHT BREAST

Incision used:

Horizontal ☐

Lateral ☐

Vertical ☐

Wise pattern ☐

IMF ☐

Weight of specimen (g) _____

Axillary Procedure:

None ☐ SNB☐ Sample ☐

Clearance ☐

Expander Yes ☐ No ☐

Brand _____

Initial volume inserted _____

Implant Yes ☐ No ☐

Brand _____

Implant inserted _____

NPWT Dressing used Yes ☐ No ☐

Strattice size _____

Histology (TNM) _____

Operative time (mins) _____

Axillary Procedure:

None ☐ SNB☐ Sample ☐

Clearance ☐

Expander Yes ☐ No ☐

Brand _____

Initial volume inserted _____

Implant Yes ☐ No ☐

Brand _____

Implant inserted_____

NPWT Dressing used Yes ☐ No ☐

Strattice size _____

Histology (TNM) _____

Operative time (mins) _____

Antibiotic use: Peri-op Yes ☐ No ☐

Post-op Yes ☐ No ☐

Adjuvant treatment

Chemotherapy	Yes ☐	No ☐
Herceptin	Yes ☐	No ☐
Chest wall Radiotherapy	Yes ☐	No ☐
Endocrine	Yes ☐	No ☐

Post-op complications

Suspected Infection 1a ☐ 1b ☐ 1c ☐ No ☐

Antibiotics given Yes ☐ No ☐

Wound dehiscence/delayed healing 1a ☐ 1b ☐ No ☐

Further description

_____
_____
_____

Seroma Yes ☐ No ☐ Required aspiration Yes ☐ No ☐

No. of aspirations _____

Implant loss Yes ☐ No ☐

Date _____

Details

_____
_____
_____
_____

Readmission

_____

Within 30 days: Yes ☐ No ☐

Re-operation: Yes ☐ No ☐

Planned: Yes ☐ No ☐

Details_____
_____
_____
_____
_____
_____

Unplanned: Yes ☐ No ☐

Reason:

Haematoma ☐ Infection ☐ Capsular contracture ☐
Malposition ☐ Rupture ☐ Asymmetry ☐
Patient request style/size change ☐ Other ☐

Date (s) _____

Details_____

_____

_____

_____

_____

_____

STUDY: BROWSE

Clinical Assessment

Date of visit:

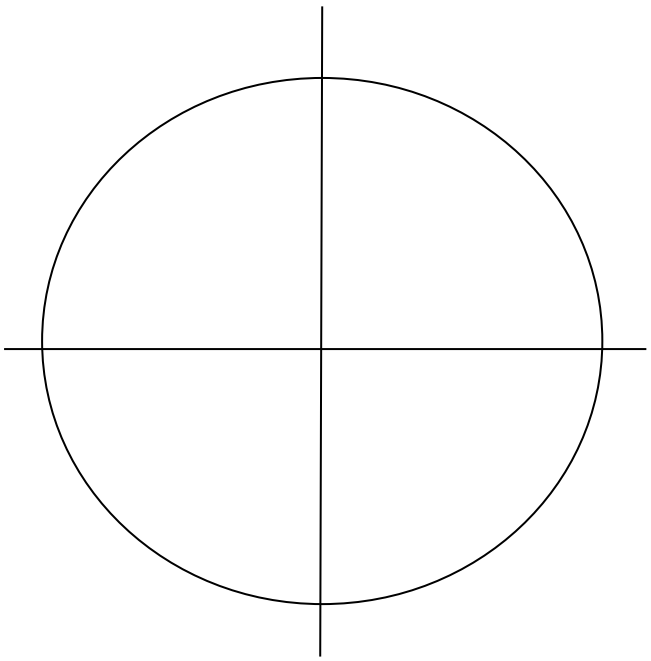
Chaperone:

Baker Grade

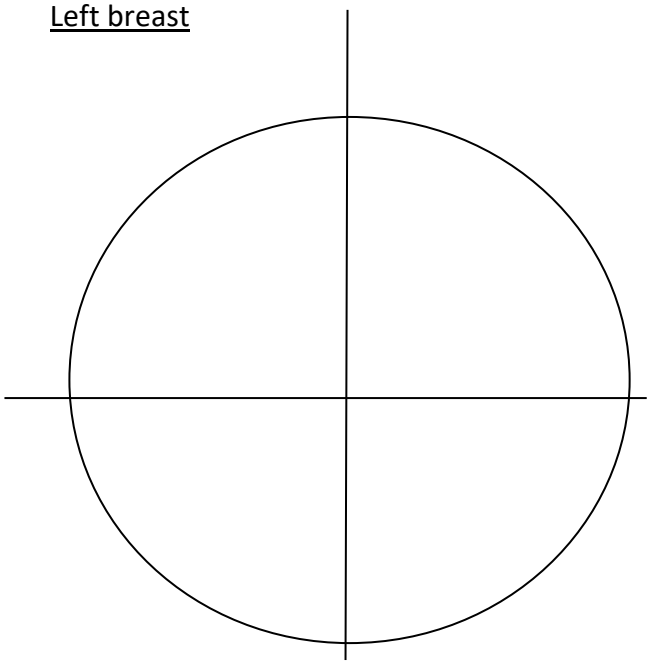
LEFT BREAST					RIGHT BREAST				
Research Fellow	1 ☐	2 ☐	3 ☐	4 ☐	Research Fellow	1 ☐	2 ☐	3 ☐	4 ☐
Patient	1 ☐	2 ☐	3 ☐	4 ☐	Patient	1 ☐	2 ☐	3 ☐	4 ☐

Tonometer Readings

Right breast



Left breast



PROMs Questionnaire given Yes ☐ No ☐

Medical Photographs Yes ☐ No ☐

Data set complete Yes ☐ No ☐

Signed _____

Date _____

7.4 Medical illustration SOP

Document Number	BMP01
Date Created	15/09/2016
Version	1.0
Status	
Date Approved	
Next review date	
Approved by	Helen Carruthers, Medical Illustration, UHSM
Author	Rebecca Wilson, Research Fellow, UHSM

1. Purpose

To clearly define the role of Medical Illustration Department in the BROWSE study. This document is to further clarify the information provided in the BROWSE Study protocol.

2. Scope

For Medical Illustration Department staff and Research Personnel coordinating the research at each site.

3. Summary

Medical Illustration department are to take relevant photographs after the clinical assessment visit.

4. Procedure

- Patient consents to participate in BROWSE Study including having photographs taken
- Use BROWSE sticker on the Medical Illustration request form, so the team know they are part of the study
- Medical illustration to go through their standard consent procedure
- Three views to be taken, following the Institute of Medical Illustrators National Guidelines stating that the standard breast views illustrate the chin down to the navel, ensuring the shoulders are visible. Ask patients to place their hands “loosely” behind their back, tie back any hair that covers the shoulders or neckline in order to expose the anatomical reference points
    - Anterior – sternum in centre of the frame
    - Right and left lateral – parallel to the coronal plane
- Vertical format
- Please use the same off-white (or similarly neutral) background for each patient
- Report as per standard care
- Annonymise photo with initials and study participant number (found on BROWSE sticker on request form) only and save electronically
- At the end of study please provide all annonymised photos on a disc to the research fellow (Rebecca Wilson)

7.5 Aesthetic assessment SOP

Document Number	BAS01
Date Created	02/08/2017
Version	1.0
Status	
Date Approved	
Next review date	
Approved by	James Harvey, Consultant, UHSM
Author	Rebecca Wilson, Research Fellow, UHSM

1. **Purpose**
   To clearly define the role of those scoring the photographs for the cosmetic assessment section of the BROWSE Study. This document is to further clarify the information provided in the BROWSE Study protocol

2. **Scope**
   For the blinded panel chosen to score each anonymous photograph taken of patients who have undergone implant based breast reconstruction and participated in the BROWSE Study

3. **Summary**
   The panel of assessors are asked to score using the below scale the photographs displayed on the power point presentation of participants of the BROWSE Study

4. **Procedure**
   - Familiar self with the following 10-point Visser scale (62)

Characteristic	Scale
Breast volume	1 (very dissatisfied) 2 3 4 5 (very satisfied)
Breast shape	
Breast symmetry	
Breast scars	
Nipple/NAC	
General satisfaction	1 (extremely dissatisfied) 2 3 4 5 6 7 8 9 10 (extremely satisfied)

- Extract the PDF document from the USB/DVD using the password provided
- The photos are displayed with the participant study number in the top left corner, ensure this correlates with the row you are filing out
- The photos will be displayed one per slide (front and 2x lateral)
- Fill out the scoring chart (appendix 1) using the Visser scale above
- Give a score for breast volume, breast shape, breast scars, nipple/NAC and general satisfaction for each breast but only once score for symmetry looking at the breasts together

Appendix 1

Study No.	**Side L/R**	**Breast volume**	**Breast shape**	**Breast symmetry**	**Breast scars**	**Nipple/NAC**	**General satisfaction**
		1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	
		1 2 3 4 5	1 2 3 4 5		1 2 3 4 5	1 2 3 4 5	
		1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	
		1 2 3 4 5	1 2 3 4 5		1 2 3 4 5	1 2 3 4 5	
		1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5	
		1 2 3 4 5	1 2 3 4 5		1 2 3 4 5	1 2 3 4 5	

7.6 Breast Q (post-operative reconstruction module)

The following questions are about your breasts and breast reconstruction surgery. After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. With your breasts in mind, in the past 2 weeks, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. a. How you look in the mirror clothed?	1	2	3	4
a. b. The shape of your reconstructed breast(s) when you are wearing a bra?	1	2	3	4
a. c. How normal you feel in your clothes?	1	2	3	4
a. d. The size of your reconstructed breast(s)?	1	2	3	4
e. Being able to wear clothing that is more fitted?	1	2	3	4
f. How your breasts are lined up in relation to each other?	1	2	3	4
g. How comfortably your bras fit?	1	2	3	4
h. The softness of your reconstructed breast(s)?	1	2	3	4
i. How equal in size your breasts are to each other?	1	2	3	4
j. How natural your reconstructed breast(s) looks?	1	2	3	4
k. How naturally your reconstructed breast(s) sits/hangs?	1	2	3	4
l. How your reconstructed breast(s) feels to touch?	1	2	3	4
m. How much your reconstructed breast(s) feels like a natural part of your body?	1	2	3	4
n. How closely matched your breasts are to each other?	1	2	3	4
o. How your reconstructed breast(s) look now compared to before you had any breast surgery?	1	2	3	4
p. How you look in the mirror unclothed?	1	2	3	4

Please check that you have answered all the questions before going on to the next page

This question is about breast reconstruction using IMPLANTS. If you do not have an implant(s) please skip to question 3. If you do have an implant(s), please answer question 2 below.

2. In the past 2 weeks, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. The amount of rippling (wrinkling) of your implant(s) that you can see?	1	2	3	4
b. The amount of rippling (wrinkling) of your implant(s) that you can feel?	1	2	3	4

3. We would like to know how you feel about the outcome of your breast reconstruction surgery. Please indicate how much you agree or disagree with each statement:

	Disagree	Somewhat Agree	Definitely Agree
a. Having reconstruction is much better than the alternative of having no breast(s).	1	2	3
b. I would encourage other women in my situation to have breast reconstruction surgery.	1	2	3
c. I would do it again.	1	2	3
d. I have no regrets about having the surgery.	1	2	3
e. Having this surgery changed my life for the better.	1	2	3
f. The outcome perfectly matched my expectations.	1	2	3
g. It turned out exactly as I had planned.	1	2	3

Please check that you have answered all the questions before going on to the next page

4. With your breasts in mind, in the past 2 weeks, how often have you felt:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Confident in a social setting?	1	2	3	4	5
b. Emotionally able to do the things that you want to do?	1	2	3	4	5
c. Emotionally healthy?	1	2	3	4	5
d. Of equal worth to other women?	1	2	3	4	5
e. Self-confident?	1	2	3	4	5
f. Feminine in your clothes?	1	2	3	4	5
g. Accepting of your body?	1	2	3	4	5
h. Normal?	1	2	3	4	5
	1	2	3	4	5

i.	Like other women?					
j.	Attractive?	1	2	3	4	5

5. Thinking of your sexuality, since your breast reconstruction, how often do you generally feel:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time	Not Applicable
a.	Sexually attractive in your clothes?	1	2	3	4	5	N/A
b.	Comfortable/at ease during sexual activity?	1	2	3	4	5	N/A
c.	Confident sexually?	1	2	3	4	5	N/A
d.	Satisfied with your sex-life?	1	2	3	4	5	N/A
e.	Confident sexually about how your breast(s) look when unclothed?	1	2	3	4	5	N/A
f.	Sexually attractive when unclothed?	1	2	3	4	5	N/A

Please check that you have answered all the questions before going on to the next page

6. In the past 2 weeks, how often have you experienced:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Neck pain?	1	2	3	4	5
b.	Upper back pain?	1	2	3	4	5
c.	Shoulder pain?	1	2	3	4	5
d.	Arm pain?	1	2	3	4	5
e.	Rib pain?	1	2	3	4	5
f.	Pain in the muscles of your chest?	1	2	3	4	5
g.	Difficulty lifting or moving your arms?	1	2	3	4	5
h.	Difficulty sleeping because of discomfort in your breast area?	1	2	3	4	5
i.	Tightness in your breast area?	1	2	3	4	5
j.	Pulling in your breast area?	1	2	3	4	5
k.	Nagging feeling in your breast area?	1	2	3	4	5
l.	Tenderness in your breast area?	1	2	3	4	5
m.	Sharp pains in your breast area?	1	2	3	4	5
n.	Shooting pains in your breast area?	1	2	3	4	5
o.	Aching feeling in your breast area?	1	2	3	4	5

p. Throbbing feeling in your breast area?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

This question is about NIPPLE reconstruction. If you did <u>not</u> have nipple reconstruction, please skip to question 11. If you did have nipple reconstruction, please answer question 10 below.

10. In the past 2 weeks, how <u>satisfied or dissatisfied</u> are you with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. The shape of your reconstructed nipple(s)?	1	2	3	4
b. How your reconstructed nipple(s) and areola(s) look?	1	2	3	4
c. How natural your reconstructed nipple(s) look?	1	2	3	4
d. The color of your reconstructed nipple/areolar complex?	1	2	3	4
e. The height (projection) of your reconstructed nipple(s)?	1	2	3	4

Please check that you have answered all the questions before going on to the next page

11. How satisfied or dissatisfied were you with the information you received from your plastic surgeon about:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How the breast reconstruction surgery was to be done?	1	2	3	4
b. Healing and recovery time?	1	2	3	4
c. Possible complications?	1	2	3	4
d. The options you were given regarding types of breast reconstruction?	1	2	3	4
e. The options you were given regarding timing of your breast reconstruction (i.e. same time as your mastectomy versus later)?	1	2	3	4
f. The pros and cons of the timing of your breast reconstruction?	1	2	3	4
g. How long the process of breast reconstruction would take from start to finish?	1	2	3	4
h. What size you could expect your breasts to be after reconstructive surgery?	1	2	3	4
i. How much pain to expect during recovery?	1	2	3	4
j. What you could expect your breasts to look like after surgery?	1	2	3	4
k. How long after reconstruction surgery it would take to feel like yourself/feel normal again?	1	2	3	4
l. How the surgery could affect future breast cancer screening (e.g. mammogram, self examinations)?	1	2	3	4
m. Lack of sensation in your reconstructed breast(s) and nipple(s)?	1	2	3	4
n. What other women experience with their breast reconstruction surgery?	1	2	3	4
o. What the scars would look like?	1	2	3	4

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7.7 Capsule participant information sheet

University Hospital of South Manchester NHS
NHS Foundation Trust

Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
M23 9LT
Tel: 0161 998 7070

The Capsule Study

A study investigating the mechanisms associated with capsule formation in patients undergoing breast reconstruction with implant and acellular dermal matrix (ADM)

PARTICIPANT INFORMATION SHEET

Version 3 dated 1st June 2016

Principle Investigator: Miss Cliona Kirwan

Sponsor: University Hospital of South Manchester

We would like to invite you to take part in our study. Before you decide it is important you read this information leaflet so you can understand why this research is being done and what it will involve. Talk to others about this if you wish. One of our researchers will also talk you through it and answer any questions you may have. Take your time to decide.

Purpose of the study

When an implant is inserted into the breast, scar tissue (a capsule) forms around it. A common problem following implant-based reconstruction is capsular contracture. This is when the capsule becomes hard, potentially causing the breast to look and feel different and even sometimes causing pain.

It is reported that capsular contracture may be less in patients who under go breast reconstruction with implant and ADMs. We want to investigate further in to why this may be.

Why have I been invited?

You have had a reconstruction with an implant (or tissue expander) and ADM. As part of your treatment you require a second operation. It is during this second operation that we will take four small pieces of the capsule, which will be tested, in the laboratory.

Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

During your operation we will need to take out your current implant. At this time we will be able to see the capsule that has formed inside your reconstruction. If you take part, after the implant is taken out as part of your operation, four small pieces, approximately 5mm each, will be taken from the capsule. Two from the upper part near the muscle and 2 from the lower part near the ADM. The rest of your operation will continue as normal. These pieces will be sent to the laboratory at Manchester University for further tests. After your operation, you will be looked after the same as if you were not in the study.

What will I have to do?

The good thing about this study is that you have to do very little. In fact, you will not have to do anymore than if you were not part of the study. All you need to do is to come to hospital for your given date for surgery and we will do the rest.

Expenses and payments

There will be no extra expenses to you for taking part in the study. The study is completely voluntary and there is no payment for participating.

What are the possible disadvantages and risks of taking part?

As with all surgery, there is a small risk of bleeding. This is the case for your operation even if you do not take part in this study. However, as we are making very small extra cuts in the capsule, the risk of bleeding is very slightly increased. Throughout the operation, the surgeon will be using techniques to decrease the chance of bleeding. Large bleeding following this type of surgery is very rare, however bleeding can make the long term results of the breast reconstruction less satisfactory. Very rarely, the implant may need removing.

What are the possible benefits of taking part?

There are no direct benefits for you in taking part in this study. Although ADMs have been used in breast reconstruction since 2008; there are no big long-term studies on how it compares to traditional reconstruction

with an implant only. Taking part in this study may help other women, in the future, to make decisions about their choice of reconstruction.

What will happen if I decide I do not want to carry on with the study?

You are free to withdraw from the study at any time, without a reason. If you do withdraw, we may want to use the information we had collected up until that point.

Will my taking part in this study be kept confidential?

Yes. All of your personal data will be regarded as strictly confidential. The information collected will be kept in a locked filing cabinet or a NHS password protected computer both with restricted access. If any data does have to leave the site your information will be identified using a unique code specific to this study, so you will not be recognized.

Members of the research team will routinely access identifiable data. However, some parts of your medical records and the data collected may be looked at by authorized people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do out best to meet this duty.

What will happen to the results of the research study?

We are hoping that the results of this study will be published in peer review journals and presented at International/National Meetings. A summary of the results will be available on request. Neither you nor any of your personal information will be identifiable in the reporting of the results.

Who is organising and funding this research?

The Capsule Study is organised by leading breast surgeons at the University of Manchester and University Hospital of South Manchester, together with researchers at LifeCell EMEA Ltd (the company that makes Strattice™ Tissue Matrix). Your doctor will not receive any personal financial payment if you take part.

This research is being paid for by LifeCell EMEA Ltd. The National Health Service Research and Development Executive are paying for the extra nursing and administrative costs incurred by the hospitals.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by The North West Research Ethics Committee.

Further information and contact details

If you require any further information regarding:

1. General information about research please do not hesitate to contact South Manchester NHS Foundation Trust Research and Development Department on 0161 291 4651
2. Specific information about this research project, advice as to whether to participate or if you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. They can be contacted on 0161 998 7070, during 9am – 5pm, Monday to Friday, if you ask to be put through to the Nightingale Centre.
3. If you would like to discuss the study with someone who is not involved in the study, please contact your local Patient Advice and Liaison Service (PALS) at pals@uhsm.nhs.uk or telephone 0161 291 5600.

Thank you for taking the time to read this

7.8 Capsule Study CRF

CASE REPORT FORM

Capsule Study

Clinical Trial Site Name: UHSM

Chief Investigator: Miss. C. Kirwan

Co-investigators: Mr. A. Bayat, Mr J. Harvey, Miss R. Teasdale

Participant Initials: _____

Participant Study Number:

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator signature:_____

STUDY: Capsule

Baseline Visit 1

Date of visit: **Centre: UHSM**

Screening Inclusion Criteria **ALL ANSWERS SHOULD BE COMPLETED YES**

		Yes	**No**
1	Patient is female >18	☐	☐
2	Patient is capable of informed consent	☐	☐
3	Further surgery after implant based breast reconstruction with lower pole coverage with Strattice	☐	☐

Screening Exclusion Criteria **ALL ANSWERS SHOULD BE COMPLETED NO**

		Yes	**No**
1	Delayed reconstruction	☐	☐
2	Total cover Strattice reconstruction	☐	☐

Confirm eligibility to study: Yes ☐ No ☐

Date of consent: (Version……. Date……..)

Baseline details:	
Age at registration	☐☐
Height (m)	☐☐☐
Weight (Kg)	☐☐☐
BMI	☐☐. ☐ kg/m^2

At the time of the initial surgery:

Relevant Past Medical History

Relevant Medications

Steroids	
Anti-coagulants	

History of abnormal scarring: Yes ☐ No ☐

Diabetes: Yes ☐ No ☐

Smoker: Yes ☐ No ☐ Ex ☐

Previous chest wall radiotherapy Yes ☐ No ☐ Details

_____

CLINICAL DETAILS

LEFT BREAST

Date of original reconstructive surgery surgery

_____

Reason for surgery:

Risk reducing ☐ Cancer ☐

Prosthesis used:

Expander Yes ☐ No ☐

Brand _____

Initial volume inserted _____

Implant Yes ☐ No ☐

Brand _____

Implant inserted _____

Adjuvant treatment

Chest wall Radiotherapy Yes ☐ No ☐

Post-op complications (occurring after original reconstruction or subsequent revisions prior to this one)

Infection Yes ☐ No ☐

Wound dehiscence/delayed healing Yes ☐ No ☐

Further description

_____

_____

_____

RIGHT BREAST

Date of original reconstructive surgery

_____

Reason for surgery:

Risk reducing ☐ Cancer ☐

Expander Yes ☐ No ☐

Brand _____

Initial volume inserted _____

Implant Yes ☐ No ☐

Brand _____

Implant inserted_____

Seroma Yes ☐ No ☐ Required aspiration Yes ☐ No ☐

Requiring drain >2/52 Yes ☐ No ☐

Implant loss Yes ☐ No ☐

Date _____

Details

_____

_____

_____

_____

Further surgical procedures (between now and the original reconstruction) Yes ☐ No ☐

Date(s)_____

Details_____

_____

_____

_____

_____

Current Procedure

Date_____

Details_____

_____

_____

_____

Reason:

Second stage expander to implant ☐ Capsular contracture ☐

Malposition ☐ Patient request style/size change ☐ Rupture ☐

Asymmetry ☐ Other ☐ -

_____

Clinical Assessment

Date of visit:

Chaperone:

Baker Grade

LEFT BREAST		RIGHT BREAST	
Research Fellow	1 ☐ 2 ☐ 3 ☐ 4 ☐	Research Fellow	1 ☐ 2 ☐ 3 ☐ 4 ☐
Patient	1 ☐ 2 ☐ 3 ☐ 4 ☐	Patient	1 ☐ 2 ☐ 3 ☐ 4 ☐

Tonometer Readings

LUOQ _____ LUIQ _____ LLOQ _____ LLIQ _____

RUOQ _____ RUIQ _____ RLOQ _____ RLIQ _____

Data set complete **Yes** ☐ **No** ☐

Signed _____

Date _____