ASERNIP-S

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of New
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Rapid Review

Breast prosthesis implantation for reconstructive and cosmetic surgery: a rapid review

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The Rapid Review of
Breast prosthesis implantation for reconstructive and cosmetic surgery was ratified by the ASERNIP-S Review Group on
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ASERNIP-S rapid review

Disclaimer

This document is not comprehensive. Rather, this is a rapid systematic review in which the scope or methodology has been limited in one or more areas to shorten the timeline for its completion. For this document, limits were applied by restricting the specific clinical questions asked following the requirements of the specific review topic, together with clinical guidance from protocol surgeons.

The methodology used for the rapid review is described in detail, including the limits made for this particular topic. Modifications were made in at least one of the following areas: search strategy, inclusion criteria, assessment of study quality and data analysis. It is considered that these amendments would not significantly alter the overall findings of the rapid review when compared to a full systematic review.

Therefore, this rapid review is a limited evidence-based assessment that is based on a focused systematic search of studies published in the peer-reviewed literature. As a result, this rapid review may be used to inform certain questions on the specific review topic.

For a more comprehensive understanding of this topic, a broader analysis of the literature may be required. As such, all readers of this document should be aware of the limitations of this review.

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Shortened forms

AIHW	Australian Institute of Health and Welfare
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures - Surgical
CI	confidence interval
CRD	Centre for Reviews and Dissemination
FDA	Food and Drug Administration
IHE	Institute of Health Economics
IRG	International Review Group
MeSH	Medical Subject Headings
MRI	Magnetic Resonance Imaging
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NR	not reported
nRCT	nonrandomised controlled trial
NS	not significant
PICO	population, intervention, comparator, outcome
QoL	quality of life
RCT	randomised controlled trial
SA-HTAG	South Australian Health Technology Advisory Group
SD	standard deviation
TGA	Therapeutic Goods Administration

Executive summary

Aim and scope

This rapid review assessed the long-term safety and effectiveness of breast implantation for primary and revision breast reconstruction and augmentation, using a rapid systematic review of the literature. Articles published from 2005 and with five or more years follow-up were eligible for inclusion in this rapid review. Where authors listed the manufacturer of the implants a subgroup analyses was conducted in breast reconstruction and augmentation indications; as well as prior treatment with radiotherapy or chemotherapy in patients undergoing implantation for breast reconstruction.

Methods

Studies were identified by searching the York Centre for Reviews and Dissemination (York CRD), The Cochrane Library, EMBASE and PubMed from 1 January 2005 to 19 October 2012. Due to the rapid nature of this review, hand-searching of journals, contacting of authors for unpublished data and pearling of references from retrieved articles was not undertaken. Literature considered eligible for inclusion was restricted to English language publications. Data extraction was performed using standardised tables that were developed a priori, and a second reviewer checked the extraction tables. Critical appraisal was conducted using a standardised checklist for the appraisal of case series data.

Key results and conclusions

Due to the quality, characteristics and disparity of the literature available with duration of follow-up of five years or more, it was difficult to observe trends in the data. In addition, 17 of the 28 included studies were retrospective in design and therefore outcome assessment was dependent on the extent and accuracy of historical record keeping. This in addition to the poor methods of assessing rupture and determining patient satisfaction presented a challenge for this rapid review.

The majority of the results reported for the safety and effectiveness of breast implantation across all indications was reported as Kaplan-Meier estimates calculated based on the incidence of safety and effectiveness outcomes in a subset of study participants. Validated tools and structured assessment tools tailored to the outcomes of breast implantation, such as the Breast Q tool (Pusic et al 2009) were not used to assess patient satisfaction in the included studies. Where reported, patient satisfaction predominantly comprised patient self-assessment using surveys of varying length and content.

As rupture results for all indications were predominantly reported as Kaplan-Meier estimates it is difficult to determine from the literature the long-term incidence of rupture.

Kaplan-Meier estimates and incidence data of capsular contracture increased over time, particularly between five and 10 and up to 15 year follow-up for all indications and implant types. Silicone gel-filled implants reported the lowest estimate of capsular contracture and, wrinkling and rippling in primary reconstruction patients compared to saline-filled and permanent expander implants. In

addition, the Kaplan-Meier estimates of adverse events for primary augmentation with silicone gel-filled implants were similar to primary reconstruction patients.

Permanent expanders, used for primary and revision breast reconstruction in three studies, resulted in a higher incidence of adverse events compared to Kaplan-Meier estimates for silicone gel-filled implants for the same indications, and saline-filled implants for primary breast reconstruction. In addition, at 12.5-year follow-up all permanent expanders had been removed in the two studies reporting re-operation; and complaints included capsular contracture, poor aesthetics and deterioration in patient satisfaction.

The ability to determine the in vivo lifespan of breast implants across primary and revision breast reconstruction and augmentation was limited as the data was primarily comprised of Kaplan-Meier estimates. However, where reported incidence data compared to Kaplan-Meier estimates agreed with the trend in outcomes over time; namely, that capsular contracture, the likelihood of rupture and patient dissatisfaction all increase over time following implantation with any type of breast prostheses.

The available data suggests re-operation is typically performed within five to 10 years following implantation due to a variety of reasons ranging from dissatisfaction with the style or size of implant, or the occurrence of capsular contracture or implant rupture.

Consequently, developments in the available evidence-base for the assessment of the long-term safety and effectiveness of breast implantation should comprise prospectively designed comparative studies where data is stratified according to surgical technique and the characteristics of the implants used.

Clinical recommendations

The clinical evidence base identified is predominantly low-level evidence that does not contain sufficient clinical data to inform on the long-term safety and effectiveness of breast implantation. Consequently there is a need for data collection in a large number of women, over a long time horizon presenting a higher-level of detail about patient-relevant outcomes than is currently available. It is proposed that industry, government, surgeons and patients all have a role to play in defining and informing on the nature of data that should be collected. The results of this review would support initiatives such as the newly developed Breast Implant Device Registry as well as collaboration across registries internationally to form a consistent minimum data set.

A key outcome of this review could be the generation of a peer reviewed article summarising the current uncertainties around the long-term safety and effectiveness of breast implantation and investigating adjunct areas of clinical uncertainty such as appropriate imaging modalities and screening protocols for implant rupture.

Introduction

Media coverage regarding the manufacture of silicone gel breast implants by Poly Implant Prosthèse (PIP) (France) has raised concerns about the safety and long-term outcomes associated with silicone breast implants in Australia (TGA 2012b). Regulatory issues regarding breast implants are discussed in the results section of this review. This rapid systematic review was proposed by the South Australian Health Technology Assessment Group (SA-HTAG) and conducted in close collaboration with clinicians.

The increase in short-term efficacy of breast implantation in the 1970s and 1980s resulted in increasing numbers of women undergoing augmentation surgery (2001). Additionally, breast implantation following mastectomy is a common option for women with breast cancer. Breast implants are considered high risk (Class III) medical devices and have a limited life-span (Department of Health and Ageing 2012); however, many women assume them to be lifelong devices (The Independent Review Group (IRG) 1998).

The risk of implant rupture, capsular contracture and wrinkling and rippling increases with time, yet a recommended in vivo life-span of these implants has not been determined. The SA-HTAG was interested in the long-term safety and effectiveness of any breast prosthesis implant for reconstructive and cosmetic purposes, irrespective of manufacturer. In relation to the long term safety and effectiveness of breast implants, of particular interest was the incidence of implant rupture, capsular contracture (tightening of the capsule that surrounds the implant due to scar tissue formation that can lead to hardening, disfigurement and pain) and implant removal/revision over time, as well as patient satisfaction. This data is currently being captured in the new Australian Breast Implant Registry in order to track the in vivo lifespan of breast implants over time. Such data would also be able to inform guidance on the best time intervals to screen breast implants (for example with magnetic resonance imaging) and whether it is best to remove implants prior to rupture due to the complications which may arise following rupture.

Rapid review methodology was employed in order to achieve a comprehensive examination of the evidence base within a limited timeframe. This involved limiting the included evidence to that of five or more years of follow-up and only articles published from 2005 onwards.

The primary objective of this rapid review was to assess the long-term clinical and quality of life outcomes following the implantation of all breast prostheses for clinical reconstructive or augmentation purposes through a systematic review of the literature. Additional sub-group analyses of outcomes were conducted: 1) by manufacturer for studies that reported the manufacturer of implants used and; 2) by preceding cancer treatment for studies that reported the outcomes of breast reconstruction following radiotherapy or chemotherapy as compared to patients who did not receive those treatments.

Background

Breast implantation: history, context and current issues

Historically, the use of breast implants has been controversial. Given the widespread use of implants for both reconstructive and cosmetic purposes, there was considerable interest in the safety of silicone gel implants. This culminated in United States (US) Food and Drug Administration (FDA) withdrawing marketing approval in 1992 due to lack of safety and effectiveness data. Local complications observed with breast implant use include rupture, pain, capsular contracture, disfigurement and serious infection. Breast implant use has additionally been considered for a variety of disease states, including connective tissue diseases (Jeeves and Cooter 2012).

The Australian Society of Plastic Surgeons (ASPS) has maintained a Breast Implant Registry (BIR) since 1998, which collects information relating to breast implant procedures. The registry was created to provide a secure and safe environment to store patient data following a breast implant procedure. However, the opt-in consent model has resulted in low participation rates since its inception , and a recent recall of breast implants from a French manufacturer has highlighted a low data capture rate (Jeeves and Cooter 2012). Due to shortcomings of the Breast Implant Registry, a new registry has been developed using international best practice in device registry design. The new Breast Device Registry will function as an opt-out consent model, with no inclusion fee for patients. The registry will offer inclusion of all implantable devices used during breast cancer reconstruction and augmentation surgery (Jeeves and Cooter 2012).

A 2009 review of health technology assessment in Australia recommended tighter post-marketing surveillance for devices of high risk or cost where there is new evidence regarding safety, or if there is public interest or controversy (Department of Health and Ageing 2009). Silicone-filled breast implants meet these criteria. The potential benefits of a more complete Breast Device Registry (Jeeves and Cooter 2012) included:

- the ability to access data on the type and size of a patient's implant in the event of revision surgery;
- in the event of a product recall or risk, patients and surgeons may be identified and contacted more easily; and
- surgeons may access their own data and monitor surgical outcomes.

The recent developments regarding the use of unlicensed silicone polymers and other compounds in the manufacturing of the PIP have once again highlighted safety concerns surrounding breast implant use. This breach in manufacturing standards may be associated with a possible increase in implant rupture rate, potentially affecting more than 6000 women in Australia who received PIP implants (Jeeves and Cooter 2012).

Outcomes and adverse events associated with breast implantation

The US Food and Drug Administration (FDA) produced an update on the safety of silicone gel-filled breast implants in 2011 and identified frequent local complications and adverse outcomes (FDA 2011a). The most frequent events included capsular contracture, implant removal (with or without replacement) and re-operation (for reasons including adverse events and patient request). The risk

of an adverse event was found to increase the longer a woman had implants and the report noted that women need to self-monitor for these local complications for the rest of their lives (FDA 2011a) although self-monitoring may not identify early complications.

Implant rupture or deflation can result from a variety of causes including mechanical trauma, surgical technique utilised during implantation, explantation or revision, or breast prosthesis defects (device failure). Silent rupture typically occurs with silicone gel-implants as a result of intracapsular rupture, in which the silicone gel remains cohesive and within the tissue capsule surrounding the implant; and is generally identified during an MRI scan rather than clinical or self-examination (palpation). However, intracapsular contracture can cause extracapsular leakage of silicone-gel slowly into the surrounding tissues if the implant is not removed. In addition, in some cases implant wrinkling and/or rippling can be an early indication of capsular contracture, and similarly to rupture or deflation, can be a result of surgical technique, implant characteristics, as well as human factors relating to attack of the implant by the immune system.

Capsular contracture is the development of a capsule of collagen tissue surrounding the breast implant as the result of an immune response by the body in reaction to a foreign body. Over time the collagen capsule hardens and tightens, resulting in contracture of the breast prosthesis and results in a hard appearance of the breast as well as pain upon palpation. Whilst the causes of capsular contracture are not known bacterial contamination, the texture of the surface of the implant, rupture of the breast implant shell and surgical technique are thought to be contributing factors.

Re-operation, also known as revision, can be undertaken for a variety of reasons including patient dissatisfaction (asymmetry, size or style of implant) or as a result of an adverse event such as infection, capsular contracture, wrinkling and/or rippling or rupture. Reasons for re-operation include:

- to correct adverse events;
- capsulotomy with or without removal of the implant for capsular contracture or wrinkling and/or rippling;
- re-operation to correct asymmetry, to change the style or size of the implant or for implant malposition or migration; and
- explantation.

Throughout the literature the term total re-operation refers to the total number of revision surgeries performed for any reason, including explantation and capsulotomy.

Patient satisfaction outcomes are affected by the type of implant selected as fill type, size, shape and texture can be tailored to each patient's request. Anatomically shaped implants can be more susceptible to poorer aesthetic outcomes as a result of implant malposition or migration compared to round implants.

Recently the Breast Q tool has been developed in order to assess patient satisfaction following breast prostheses implantation (Pusic et al 2009). The Breast Q assessment tool consists of four modules specifically tailored for breast augmentation, reconstruction or reduction in order to

evaluate the outcomes relevant to each of the different type of procedures. The tool is also comprised of a six point conceptual framework which assesses the following:

1. satisfaction with breasts;
2. satisfaction with overall outcome;
3. psychosocial well-being;
4. sexual well-being;
5. physical well-being; and
6. satisfaction with care.

With regard to systemic complications, the FDA update found no association between the use of silicone gel-filled breast implant and connective tissue disease, breast cancer or reproductive issues. However, the risk of being diagnosed with anaplastic large cell lymphoma, whilst very low, was reported to be increased (FDA 2011a). These data and recent attention regarding the PIP implants and changes to the Breast Implant Registry have highlighted gaps in current knowledge regarding the long-term efficacy and safety of silicone breast implants for reconstructive and augmentation purposes, particularly surrounding current generations of breast implants.

Breast implantation: indications and types of implant

Breast conservation therapy and mastectomy (the partial or complete surgical removal of the breast) are common options in the treatment of breast cancer. Additionally, prophylactic mastectomies are being performed more frequently due to genetic testing of women at high risk of developing breast cancer. The effects of this treatment can be harmful, both physically and psychologically. Reconstructive breast augmentation procedures have been developed to provide both a better emotional and aesthetic outcome (Serletti et al 2011). The two main techniques used are synthetic prosthesis implantation or autologous breast reconstruction. Autologous reconstruction involves the transplantation of the patient's own tissue from another region of the body in order to reconstruct the breast (Serletti et al 2011).

Synthetic implants are used more commonly than autologous reconstruction as they are less invasive and require less surgical and recovery time (Serletti et al 2011). Since their introduction in the 1960s, breast implants have undergone improvements to both the silicone shell and the filling material, for both aesthetic and safety reasons (Rozen et al 2009). There are three forms of breast implant fill available on the market: silicone gel-filled, inflatable saline-filled and a dual lumen gel/saline-filled. Silicone gel-filled, inflatable saline-filled and dual lumen gel/saline-filled implants have regulatory approval from the Therapeutic Goods Administration (TGA), the FDA and the Conformité Européene. A description and regulatory status of each type of implant is summarised in **Error! Reference source not found.**. There are currently 46 breast implant inclusions on the Australian Register of Therapeutic Goods (ARTG; Appendix A) (2012a).

Breast implants are classified according to their filling, shell type and shape as shown in Table 1.

Table 1 Characteristics and classification of breast implants

Characteristics	
Shape	Round
	Anatomical
Fill	Sterile saline liquid
	Silicone gel - silicone gels can have different degrees of cohesion or thickness
Shell type	Smooth
	Textured - textured implants have very small micropores on their external surface and are associated with a lower rate of capsular contracture
Coating	Polyurethane sponge coating is available to cover a standard silicone gel-filled implant

Silicone-filled breast implants have been classified into different generations (Peters et al 1996; IRG 1998):

- first generation implants (1963 to 1972) were characterised by firm gel fillers, thick silicone shells and a smooth surface. First generation implants are associated complications including gel bleed and capsular contracture (IRG 1998).
- Second generation implants (1972 to mid-1980s) were softer and had a thinner shells. Second generation implants are believed to be more susceptible to rupture (Peters et al 1996; IRG 1998).
- Third generation implants are characterised by thicker silicone shells which incorporate a barrier layer and were introduced in the mid-1980s. The gel bleed and capsular contracture rates are reportedly lower than with earlier implants.
- Breast implants of the latest generation have multi-layered shells filled with highly cohesive silicone gel. Developments following third generation breast implants have primarily been changes in silicone gel composition.
- Polyurethane coated implants were developed in the late 1960s and consist of a standard silicone gel-filled implant coated in polyurethane sponge. The coating was originally applied as a fixation layer however the implants were subsequently used by surgeons to mitigate the development of capsular contracture as it was believed that this occurred at a lower incidence rate due to the polyurethane coating (Taylor et al 2013). The most utilised implants were developed in the 1980s and are the Meme and Optimam styles; however in 1991 the manufacturer voluntarily withdrew these implants from the market.

Saline-filled breast implants have an outer shell made of silicone and are filled with a sterile saline solution; they may be pre-filled or filled during surgery (FDA 2011b). Marketing approval for saline-filled breast implants was granted by the FDA in 2000.

Tissue expanders are temporary devices placed subcutaneously and require periodic, incremental inflation with sterile saline in order to stretch the skin enough to allow insertion of an implant. Tissue expanders are used for breast reconstruction and can be placed beneath chest wall muscles as part of a delayed breast reconstruction or at the time of non-skin sparing mastectomy (Hudson et al 2011). The tissue expanders are replaced with an implant (saline or silicone) in a second surgery.

Some tissue expanders are designed to remain in situ when fully inflated (Hudson et al 2011; TGA 2001).

Clinical need and burden of disease

Breast reconstruction or augmentation

Breast cancer treatment is a common reason for a patient to require therapeutic breast reconstruction and in recent decades, the number of women who seek cosmetic breast augmentation surgery has also steadily increased (Didie and Sarwer 2003). According to the Australian Institute of Health and Welfare (AIHW) a total of 8,415 augmentation mammaplasty procedures were carried out in Australia during 2009-10. Of those, 7,643 were bilateral augmentation not following mastectomy, 394 were unilateral augmentation not following mastectomy, 148 were bilateral augmentation following mastectomy and 230 were unilateral augmentation following mastectomy (2011b). From 2000-01 to 2009-10, the number of bilateral augmentation mammaplasty procedures not related to mastectomy increased from 3,105 to 7,643 (AIHW 2011b). There were also 1,977 procedures for reconstruction with insertion of a tissue expander performed in 2009-10 and 7,001 procedures relating to the removal or adjustment of breast prostheses or tissue expanders. Details are shown below (Table 2). Data is sourced from the National Hospital Morbidity Database which includes data from both public and private hospitals (Australian Institute of Health and Welfare (AIHW) 2011b). Currently, cosmetic breast augmentation is performed more frequently than augmentation for reconstructive purposes (Australian Institute of Health and Welfare (AIHW) 2011a; FDA 2011a).

Table 2 Number of procedures relating to the breast (2009-2010)

Chapter	Descriptor	Number of procedures (2009-2010)	Total procedures
1753 Augmentation mammoplasty	45524-00 Augmentation mammoplasty, unilateral	394	8,415
	45527-00 Augmentation mammoplasty following mastectomy, unilateral	230	
	45527-01 Augmentation mammoplasty following mastectomy, bilateral	148	
	45528-00 Augmentation mammoplasty, bilateral	7,643	
1756 Reconstruction procedures on breast	45539-00 Reconstruction of breast with insertion of tissue expander	1,977	1,977
1758 Procedures involving removal or adjustment of breast prosthesis or tissue expander	45542-00 Removal of breast tissue expander and insertion of permanent prosthesis	1,495	7,001
	45548-00 Removal of breast prosthesis	739	
	45548-01 Removal of breast tissue expander	169	
	45548-02 Adjustment of breast tissue expander	66	
	45551-00 Removal of breast prosthesis with complete excision of fibrous capsule	557	
	45552-00 Removal of breast prosthesis with complete excision of fibrous capsule and replacement of prosthesis	1,784	
	45554-00 Removal of breast prosthesis with complete excision of fibrous capsule and replacement of prosthesis and formation of new pocket	1,966	
	45555-00 Removal of silicone breast prosthesis and replacement with other than silicone prosthesis	225	

Medicare Benefits Schedule item numbers

In Australia, while reconstructive breast augmentation is covered by the Medicare Benefits Schedule (MBS), breast augmentation for cosmetic indications is not covered, except where it can be demonstrated that surgery is indicated due to significant breast deformity or asymmetry (Medicare Australia 2012a). Table 3 details the criteria for breast augmentation procedures covered by the MBS, along with the number of claims made per annum for each item from 2007 to 2011 (Medicare Australia 2012b). Table 4 details the MBS item numbers associated with reconstructive procedures involving reconstruction with a prosthesis, as well as item numbers for the removal or adjustment of prostheses.

The number of claims reported in the tables include only those services for which a claim has been processed by Medicare Australia. They do not include services provided by hospital doctors to public patients in public hospitals or services that qualify for a benefit under the Department of Veterans' Affairs National Treatment Account (Medicare Australia 2012b).

Table 3 Breast augmentation procedures covered by the MBS

Item Number	Descriptor	Fee/Benefit	Number of Claims
45524	MAMMAPLASTY, AUGMENTATION, for significant breast asymmetry where the augmentation is limited to 1 breast (Anaes.) (Assist.)	Fee: $727.80 Benefit: $545.85 (75%)	2007: 302 2008: 400 2009: 411 2010: 384 2011: 363
45527	MAMMAPLASTY, AUGMENTATION, (unilateral), following mastectomy (Anaes.) (Assist.)	Fee: $727.80 Benefit: $545.85 (75%)	2007: 219 2008: 248 2009: 281 2010: 297 2011: 295
45528	MAMMAPLASTY, AUGMENTATION, bilateral, not being a service to which Item 45527 applies, where it can be demonstrated that surgery is indicated because of malformation of breast tissue (excluding hypomastia), disease or trauma of the breast (other than trauma resulting from previous elective cosmetic surgery) (Anaes.) (Assist.)	Fee: $1,091.60 Benefit: $818.70 (75%)	2007: 22 2008: 31 2009: 36 2010: 45 2011: 47
45559	TUBEROUS, TUBULAR OR CONSTRICTED BREAST, where it can be demonstrated, correction of by simultaneous mastopexy and augmentation of (unilateral) (Anaes.) (Assist.)	Fee: $1,115.60 Benefit: $836.70 (75%) or $1,041.90 (85%)	2007: 40 2008: 88 2009: 128 2010: 165 2011: 179

Source: Medicare Australia (2012a; 2012b) MBS: Medicare Benefits Schedule.

Table 4 Breast reconstruction procedures covered by the MBS or implant removal or adjustment procedures

Item Number	Descriptor	Fee/Benefit	Number of Claims
45539	BREAST RECONSTRUCTION (unilateral), following mastectomy, using tissue expansion - insertion of tissue expansion unit and all attendances for subsequent expansion injections (Anaes.) (Assist.)	Fee: $1,071.20 Benefit: 75% or $803.40	2007: 1,068 2008: 1,292 2009: 1,530 2010: 1,578 2011: 1,606
45542	BREAST RECONSTRUCTION (unilateral), following mastectomy, using tissue expansion - removal of tissue expansion unit and insertion of permanent prosthesis (Anaes.) (Assist.)	Fee: $613.40 Benefit: 75% or $460.05	2007: 775 2008: 961 2009: 1,180 2010: 1,251 2011: 1,353
45566	TISSUE EXPANSION not being a service to which item 45539 or 45542 applies - insertion of tissue expansion unit and all attendances for subsequent expansion injections (Anaes.) (Assist.)	Fee: $1,071.20 Benefit: 75% or $803.40	2007: 91 2008: 96 2009: 111 2010: 128 2011: 151
45548	BREAST PROSTHESIS, removal of, as an independent procedure (Anaes.) (Assist.)	Fee: $276.80 Benefit: 75% or $207.60 85% or $235.30	2007: 154 2008: 131 2009: 142 2010: 148 2011: 212
45551	BREAST PROSTHESIS, removal of, with excision of fibrous capsule (Anaes.) (Assist.)	Fee: $443.70 Benefit: 75% or $332.80	2007: 537 2008: 600 2009: 622 2010: 715 2011: 934
45552	BREAST PROSTHESIS, removal of, with excision of fibrous capsule and replacement of prosthesis (Anaes.) (Assist.)	Fee: $638.65 Benefit: 75% or $479.00 85% or $564.15	2007: 742 2008: 690 2009: 678 2010: 745 2011: 937
45554	BREAST PROSTHESIS, removal and replacement with another prosthesis, following medical complications (such as rupture, migration of prosthetic material, or capsule formation), where new pocket is formed, including excision of fibrous capsule (Anaes.) (Assist.)	Fee: $699.45 Benefit: 75% or $524.60 85% or $624.95	2007: 2,271 2008: 2,384 2009: 2,472 2010: 2,631 2011: 3,442
45555	SILICONE BREAST PROSTHESIS, removal of and replacement with prosthesis other than silicone gel prosthesis	Fee: $638.65 Benefit: 75% or $479.00	2007: 2 2008: 6 2009: 8 2010: 8 2011: 5

Source: Medicare Australia (2012a; 2012b) MBS: Medicare Benefits Schedule.

Current treatment options

Breast augmentation is an elective cosmetic procedure and autologous fat transfer is an existing option for breast augmentation as an alternative to use of a prosthesis.

For patients opting to undergo breast reconstruction options include autologous fat transfer with or without implantation of a prosthesis. In some instances, patients may elect to not undergo reconstruction of the breast.

Research areas

For the purposes of this review long-term was defined as five or more years post-surgery. The specific research questions for this review are:

1. What is the long-term safety of breast implantation for either cosmetic or reconstructive purposes?
2. What are the long-term rates of re-operation and implant removal in women receiving breast implants for either cosmetic or reconstructive purposes?
3. What is the long-term patient satisfaction following a breast implantation procedure, for either cosmetic or reconstructive purposes?
4. What is the long-term rate of rupture, deflation, capsular contracture and implant wrinkling, and/or rippling for women five or more years post-implantation?
5. Does the use of expanders affect the rate of long-term implant rupture, deflation, capsular contracture and wrinkling, and/or rippling?

Methodology

Inclusion criteria

Studies were selected for inclusion in this rapid review on the basis of the criteria outlined in Table 5.

Table 5 PICO (publication type, population, intervention, comparator, outcomes)

Characteristic	Criteria
Publication	Systematic reviews and randomised controlled trials. In the absence of higher levels of evidence, non-randomised trials and case series will be included.
Population	All women receiving breast implants for reconstructive or cosmetic purposes followed for five years or more. Patients having received an expander implant followed by breast implantation where the in situ duration of the expander prior to implantation is not reported shall be excluded. Patients who received an expander implant followed by reconstruction with autologous fat transfer shall be excluded. Studies that do not distinguish between the use of saline or silicone fill within the reported results shall be excluded. Studies that use implants known to have been recalled shall be excluded. Due to relevance to the Australian context, any literature concerning patients who received PIP implants will be summarised..
Intervention	Breast implantation with a permanent prosthesis or a permanent expander where device fill is reported.
Comparator	Breast implantation with any other market approved type of breast implant; except for PIP implants, which will be included in a sub-group analysis assessing rupture and re-operation/revision rate specifically.
Outcomes	**Effectiveness:** • Patient satisfaction, including cosmetic and psychological outcomes • Re-operation • Rate of implant removal without revision • Rate of implant removal with revision • Implant visibility (through the skin) • Deflation of implant • Chest wall deformity • Implant displacement or malposition • Scarring **Safety (adverse events):** • Implant rupture or deflation • Capsular contracture • Wrinkling and/or rippling • Infection • Extrusion • Connective tissue disease • Necrosis • Delayed wound healing • Haematoma • Calcification • Breast pain • Breast feeding difficulties • Seroma

Any cost-effectiveness analyses reported in the included studies were also included in the rapid review.

Rupture, deflation and wrinkling and/or rippling were considered adverse events for the purposes of this review as both indicate the potential for re-operation or revision procedures and may be associated with properties of the device or the surgical techniques used for implantation.

Recurrence of cancer or incidence of cancer, where reported in the included studies, has been summarised in the results; however, this does not imply a causal link between the breast prostheses or the implantation procedure and recurrence or development of cancer.

Study design

Systematic reviews alone were included if possible; if insufficient systematic review evidence was available, randomised controlled trials (RCTs) were included. Non-randomised trials and case series evidence were included in the case of no higher level evidence.

Non-systematic reviews, case reports, articles identified as preliminary reports where results were published in later versions, articles in abstract form, letters, editorials, and animal, in vitro and laboratory studies were excluded.

Systematic reviews were defined as those studies that met all of the following criteria, as defined by (Cook et al 1997):

- focused clinical question
- explicit search strategy
- use of explicit, reproducible and uniformly applied criteria for article selection
- critical appraisal of the included studies
- qualitative or quantitative data synthesis.

A study was deemed to be an RCT if the author(s) stated explicitly (usually by some variant of the term 'random' to describe the allocation procedure used) that the groups compared in the trial were established by random allocation (Higgins and Green 2011). Studies in which the method of allocation was known but was not considered strictly random (for example, alternation, date of birth and medical record number) were classified as pseudo-randomised controlled trials (Higgins and Green 2011).

Search restrictions

Included studies were restricted to those published in English between 1 January 2005 and 19 October 2012.

Literature search strategies

Databases searched

The following databases were searched: York CRD, The Cochrane Library, PubMed and EMBASE. A list of specific search terms used can be found in Appendix B.

The British Medical Journal Clinical Evidence was searched for basic clinical information with searches for ongoing trials (using ClinicalTrials.gov and the Australian Clinical Trials Registry) used when necessary (e.g. very new technology, absence of good quality RCTs, under recommendation from clinical expert). The review did not include extended searching of internet websites and conference abstracts, hand-searching of journals, contacting authors for unpublished data or pearling references from retrieved articles.

In the absence of an appropriate systematic review, searches were conducted to identify primary studies for inclusion.

Selection of studies

Two reviewers independently applied the inclusion criteria to identify potentially eligible studies based on their abstracts; these studies were retrieved as full text. The selection criteria were then applied to the retrieved studies to identify those to be appraised and included in the review. Studies that did not meet the inclusion criteria were excluded with reasons for exclusion documented (Appendix C).

Articles were selected preferentially according to the National Health and Medical Research Council (NHMRC) levels of evidence; from highest to lowest (NHMRC 2000):

- systematic literature review;
- randomised controlled trial;
- non-randomised comparative study; and
- case series.

Where there were two or more systematic reviews with identical comparators and patient populations and an overlap of at least 50% of the included studies, only the most recently published systematic review was included, unless it was less comprehensive than the earlier review. In cases where there was less than a 50% overlap of included studies between two systematic reviews for particular procedures or comparisons, both were included.

In addition, eligible RCTs published after the search end date of the most recent systematic review found for each of the population analyses were included.

Data extraction and appraisal of study methodology

For systematic reviews, a validated appraisal tool (Oxman et al 1994) was used to ascertain the quality of the reviews prior to their use, with the CONSORT statement used to assess the quality of RCT evidence (Moher et al 2010). The TREND statement was used to assess the quality of non-randomised controlled studies (Des Jarlais et al 2004). Case series evidence was critically appraised using a modified quality appraisal checklist (Institute of Health Economics (2012), with results discussed narratively.

Data from all included studies were extracted by one researcher and checked by a second using standardised data extraction tables that had been developed a priori. The studies included in the review were classified according to the NHMRC hierarchy of evidence (2000) (Table 6). Included studies were critically appraised with respect to the method of allocation, adequacy of allocation concealment, handling of losses to follow-up, and any other aspect of the study design or execution that may have introduced bias.

As the studies included in this rapid review were a deliberately restricted sample of the current peer-reviewed literature on this topic (resulting from limits on publication type and date), formal statistical pooling (meta-analysis) was not performed.

Table 6 National Health and Medical Research Council hierarchy of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

Source: National Health and Medical Research Council (2000).

The overall body of research evidence was assessed and synthesised to address each clinical question according to Table 7. A rating from excellent to poor was assigned to the evidence, considering each of the components outlined in the table below (Table 7).

Table 7 Body of evidence assessment matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Volume of evidence	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population	population/s studied in the body of evidence are similar to the target population	population/s studied in body of evidence different to target population but it is clinically sensible to apply this evidence to target population	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Peer reviewed literature

A total of 28 studies were included in this rapid review; of which 13 assessed primary breast reconstruction, four assessed revision breast reconstruction and one addressed reconstruction (primary or revision not specified). Five studies addressed primary augmentation, six addressed revision augmentation and four addressed augmentation (primary or revision not specified). Primary or revision reconstruction for mixed (augmentation or reconstruction) indications was reported in three studies.

Implant characteristics and implantation site are listed according to study author in Table 8. A Quorum flowchart outlining the study selection and inclusion process is depicted in Figure 1.

Results are reported according to indication and the type of implant.

Allergan and Mentor studies extracted from the FDA report "Update on the Safety of Silicone Gel-Filled Breast Implants" (FDA 2011a)

The FDA approval of Allergan's Natrelle Silcone Gel-Filled Breast Implants and Mentor's MemoryGel Silicone Gel-Filled Breast Implants in November 2006 were based on manufacturer's clinical studies, called core studies, which followed hundreds of women with silicone gel-filled breast implants for three (Mentor) or four (Allergan) years. As conditions of its approval, the FDA required Allergan and Mentor to conduct six post-approval studies, one of these included a core post-approval study to gather data on longer-term safety and effectiveness (10 years post-implantation) among those participants enrolled in the studies conducted prior to approval and to evaluate the effectiveness of magnetic resonance imaging (MRI) screening in detecting implant rupture.

A total of 715 patients were enrolled in the Allergan core study and 1,008 were enrolled in the Mentor core study. Each study assigned participants to either an MRI group or a non-MRI group. All participants (MRI group and non-MRI group) received MRIs any time there were symptoms of rupture. The results of these core post-approval studies were included in the FDA report "Update on the Safety of Silicone Gel-Filled Breast Implants" (FDA 2011a). At the time of the report the Allergan core study, which commenced 20 months prior to the Mentor study, had a 10 year post-implant follow-up of 66 per cent and the Mentor Core Study had a post-implant follow-up at eight years of 58 per cent.

Data from the two post approval studies was extracted and included in this rapid review. Data from the post-approval studies is reported separately to the data available in the peer reviewed literature.

Kaplan-Meier estimates

The majority of all results were reported as Kaplan-Meier estimates with 95 per cent confidence intervals. The Kaplan-Meier procedure is a method of estimating time-to-event in the presence of censored cases. The model is based on estimating conditional probabilities at each time point when an event occurs and estimating the survival rate at each point in time. This method is predominantly used in survival analyses.

The Kaplan-Meier analysis assumes that the probability of the event depends only on time. Therefore little can be inferred about the impact of other factors on outcomes of interest. Additionally, in the case of breast implantation the occurrence of many complications can be considered competing risks and hence the results may be overestimated.

Table 8 Characteristics of breast prostheses implanted in the peer reviewed literature, grouped by indication

Author	Indication		Product name	Manufacturer	Filling	Lumen	Surface	Coating	Shapes	Prostheses implantation
Chew et al 2007	Primary reconstruction		Siltex 25 Expander	Becker	Expander saline and silicone gel	Double	Textured	None	Anatomical and round	Sub-muscular (post mastectomy) and sub-glandular (congenital)
Gui et al 2008	Primary reconstruction	Revision reconstruction	McGhan 150 Expander	Inamed	Expander saline and silicone gel	NR	Textured	None	Anatomical and round	Sub-muscular, latissimus dorsi
Benediktsson & Perbeck et al 2006	Primary reconstruction	Revision reconstruction	Siltex	Mentor	Expander - saline	NR	Textured	None	Round	Sub-cutaneous
			McGhan MicroCell	Inamed	Expander - saline	NR	Textured	None	Anatomical and round	Sub-cutaneous
Cicchetti et al 2006	Primary reconstruction	Revision reconstruction	McGhan 150 Expander	Inamed	Expander saline and silicone gel	Double	Textured	None	Anatomical	Sub-muscular, latissimus dorsi
Heden et al 2006a	Primary augmentation	Revision augmentation	McGhan 410 Cohesive	Inamed	Silicone-gel	NR	Textured	None	Anatomical and round	NR
Dancey et al 2012	Primary augmentation		Eurosilicone SAS	Eurosilicone	Silicone-gel	NR	Textured and smooth	None	Round	Sub-glandular
			GFX-EHP	Nagor	Silicone-gel	NR	Textured	None	Round	Sub-glandular
			McGhan 410 Cohesive	Inamed	Silicone-gel	NR	Textured	None	Anatomical and round	Sub-glandular

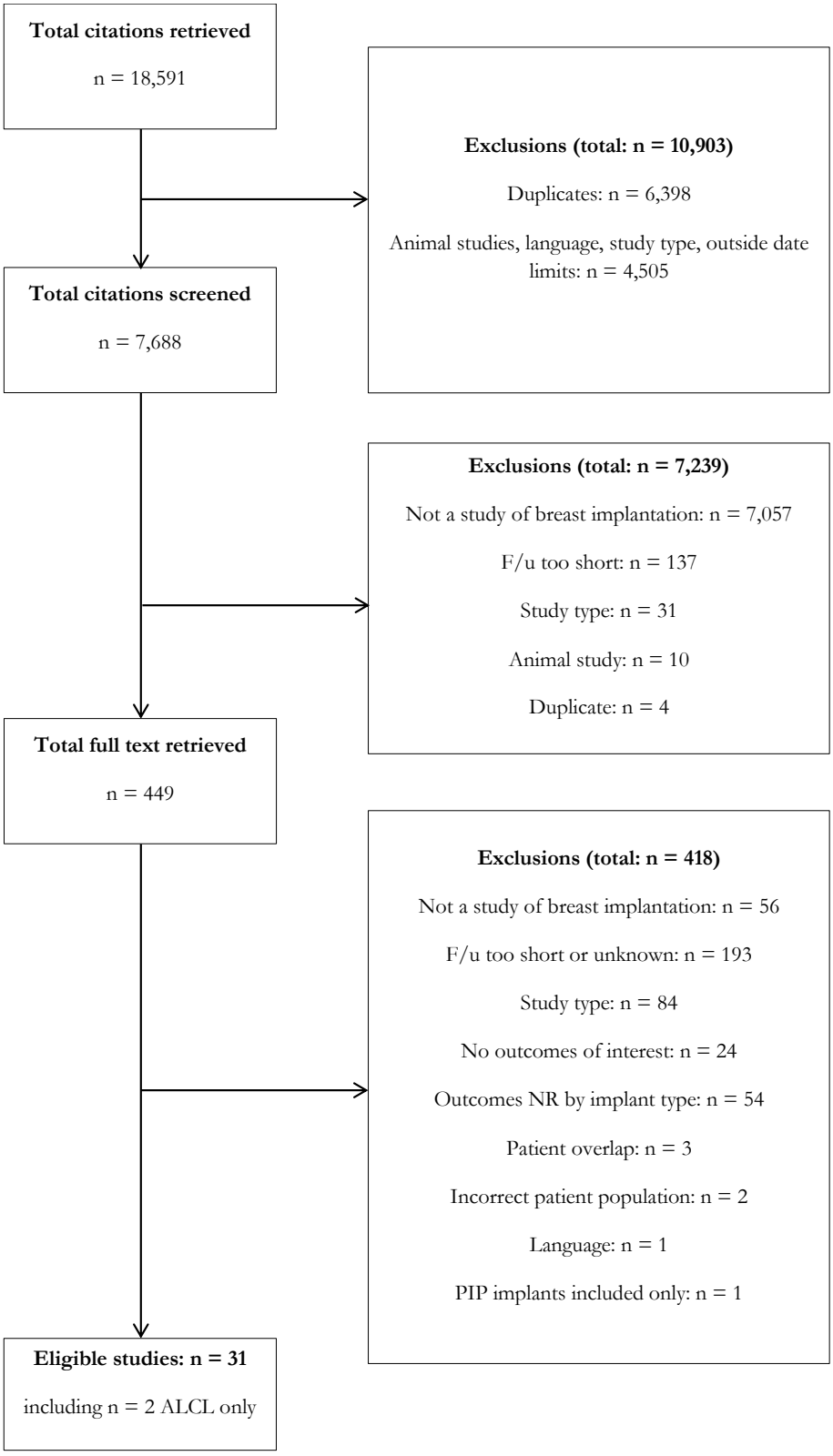
Author	Indication	Product name	Manufacturer	Filling	Lumen	Surface	Coating	Shapes	Prostheses implantation
		Silimed	Eurosurgical	Silicone-gel	NR	Textured and smooth	None	Anatomical and round	Sub-glandular
		Misti Gold	Bioplasty	polyvinylpyrrolidone-hydrogel	NR	Textured	None	NR	Sub-glandular
		Siltex	Mentor	Expander saline and silicone gel	Double	Textured	None	Anatomical and round	Sub-glandular
Collis et al 2007	Primary augmentation	Siltex	Mentor	Expander saline and silicone gel	Double	Textured	None	Anatomical and round	Sub-glandular
Pan et al 2012	Primary augmentation	NR	NR	Saline	NR	NR	None	NR	Sub-glandular, sub-muscular, unknown
		NR	NR	Silicone-gel	NR	NR	Polyurethane	NR	Sub-glandular, sub-muscular, unknown
		NR	NR	Expander saline and silicone gel	NR	NR	None	NR	Sub-glandular, sub-muscular, unknown
Pfieffer et al 2009	Primary augmentation	Polytech	Polytech-Silimed Europe	Saline outer and silicone gel inner	Double	Textured	None	NR	Sub-muscular, sub-glandular
				Silicone-gel	Single	Textured	None	NR	Sub-muscular, sub-glandular
Stevens et al 2005	Primary augmentation	Siltex	Mentor	Expander saline and silicone gel	Double	Textured	None	NR	Sub-pectoral

Author	Indication		Product name	Manufacturer	Filling	Lumen	Surface	Coating	Shapes	Prostheses implantation
Spear et al 2007	All indications		Inamed Silicone gel Breast Implant	Allergan	Silicone-gel	Single	Textured and smooth	None	Anatomical and round	Sub-cutaneous, sub-glandular, sub-muscular, sub-tissue flap
Hammond et al 2012	All indications		MemoryShape Contour Profile Gel CPG	Mentor	Silicone-gel	Single	Textured	None	Anatomical	Sub-glandular, sub-muscular, sub-pectoral, unknown
Levi et al 2007	All indications		Mentor Saline Breast Implant (style NR).	Mentor	Expander - saline	NR	Textured	None	Anatomical	Latissimus dorsi, TRAM flap
de la Pena-Salcedo et al 2012	Primary augmentation Primary reconstruction	Revision augmentation	Silimed	Silimed	Silicone-gel	Single	Textured	Polyurethane	Anatomical and round	Sub-glandular
Heden et al 2006b	All indications		Inamed Silicone Gel Implant 45, 110, 120	Inamed	Silicone-gel	Single	Textured and smooth	None	Anatomical and round	NR
Murphy et al 2009	All indications		Natrelle	Allergan	Silicone-gel	Single	Textured and smooth	None	Anatomical and round	NR
Walker et al 2009	All indications		Natrelle	Allergan	Saline	Single	Textured and smooth	None	Anatomical and round	Sub-cutaneous, sub-glandular, sub-muscular

Author	Indication	Product name	Manufacturer	Filling	Lumen	Surface	Coating	Shapes	Prostheses implantation
Cuningham & McCue 2009	All indications	Mentor MemoryGel	Mentor	Silicone-gel	Single	Textured and smooth	None	Round	NR
Araco et al 2007	All indications	Eurosilicone	Eurosilicone	Silicone-gel	Single	Textured	None	Anatomical and round	Sub-glandular, sub-fascial, sub-muscular, dual plane.
		Mentor	Mentor	Silicone-gel	Single	Textured	None	Anatomical and round	Sub-glandular, sub-fascial, sub-muscular, dual plane.
		PIP	PIP	Silicone-gel	Single	Textured	None	Anatomical and round	Sub-glandular, sub-fascial, sub-muscular, dual plane.
Heden et al 2009	All indications	Natrelle 410	Allergan	Silicone-gel	Single	Textured	None	Anatomical	Sub-glandular, sub-muscular, unknown
Maxwell et al 2012	All indications	Natrelle 410	Allergan	Silicone-gel	Single	Textured	None	Anatomical	Sub-cutaneous, sub-glandular, sub-muscular, sub-tissue flap

NR, not reported; PIP, poly implant prostheses; TRAM, transverse rectus abdominis myocutaneous; all indications, reconstructive or augmentation.

Figure 1 Quorum flow chart



F/u, follow-up; NR, not reported; ALCL, anaplastic large cell lymphoma; PIP, poly implant prostheses.

Reconstructive indication

Description of the included peer reviewed studies

A total of 14 studies which reported outcomes in patients undergoing breast implantation for reconstructive purposes were included in this review and grouped:

- primary reconstruction with saline-filled implants;
- primary reconstruction with silicone-filled implants;
- primary reconstruction with permanent expanders;
- revision reconstruction with silicone-filled implants; and
- revision reconstruction with permanent expanders.

Overall the included studies were disparate in the level of detail regarding the intervention and outcomes measured. Of the 14 studies, 13 were level IV case series data and one was level III-2 evidence (Le et al 2005). Only the treatment arm of the level III-2 study was considered in this review as the control group (women without implants from the Surveillance Epidemiology and End Results (Le et al) database) did not meet the PICO criteria. Four studies used saline-filled prostheses, six studies used silicone-filled breast implants and four used permanent expanders (Table 9). The range of follow-up in studies that used saline-filled implants was five to 12.4 years, with a total of 493 patients receiving implants for reconstructive purposes. The range of follow-up in studies of silicone-filled breast implants was six to 14.9 years and a total of 1,081 patients received implants for reconstructive purposes in those studies. The follow-up periods of studies, which used permanent expanders ranged from five years to 12.5 years with at least 110 patients receiving permanent expanders for reconstructive purposes (patient numbers not reported in one study). Table 9 provides a breakdown of the included studies and an overview of the outcomes reported by indication and device.

Two studies (Cunningham and McCue 2009; Spear et al 2007) included in this rapid review reported on patient cohorts included in the FDA update on the safety of silicone-filled breast implants (FDA 2011a). The FDA update reported eight and 10 year follow-up from the Allergan and Mentor studies (FDA 2011a). The additional information provided in the FDA update has been reported in the results; however, it should be noted that these data are not available in the peer-reviewed literature.

Benediktsson & Perbeck (2006) and Goh et al (2012) reported the use of radiation therapy prior to breast reconstruction. Chew et al (2010) reported prior and concurrent radiation therapy use in patients undergoing breast reconstruction. Cicchetti 2006 included patients undergoing radiotherapy alone or in association with chemotherapy, these patients accounted for 27 per cent of patients.

Table 9 Descriptive characteristics of the included peer reviewed studies, reconstructive indication

Study Country	Level of evidence[a] (P or R)	Manufacturer sponsored	Patient overlap	N (Ni)	Follow-up (years)	Losses to follow-up	Included for			
							Safety	Re-operation	Other effectiveness	Patient satisfaction
SALINE										
Primary reconstruction										
Benediktsson & Perbeck (2006) Sweden	IV (P)	×	NR	107 (145)	5	20/107	✓	✓	×	×
Le et al (2005) United States	III-2 (R)	×	NR	149	12.4[b]	894/5862 of initial cohort	×	✓	×	×
Levi et al (2008) United States	IV (R)	✓	NR	NR (175)	10	NR	✓	×	×	×
Walker et al (2009) United States	IV(P)	✓	NR	237 (316)	5,10	43/237	✓	✓	✓	✓
SILICONE										
Primary reconstruction										
Le et al (2005) United States	III-2 (R)	×	NR	333	12.4[b]	894/5862 of initial cohort	×	✓	×	×
Hammond et al (2012) United States	IV (P)	✓	NR	191 (328)	6	At six years: 31%	✓	✓	✓	✓
Spear et al (2007) United States	IV (P)	✓	✓	98 (127)	6	Non-compliance at six years 19%	✓	✓	✓	✓
Cunningham & McCue (2009) United States	IV (P)	✓	NR	251 (NR)	6	Non-compliance at six years 39%	✓	✓	×	✓
Maxwell et al (2012) United States	IV (P)	✓	NR	225 (351)	6	Non-compliance at six years 27%	✓	✓	✓	✓
Tarantino et al (2006) Switzerland	IV(R)	×	NR	68 (NR)	14.9	Only 51 patients had clinical follow-up	✓	✓	×	✓
Yiacoumettis et al (2005) Greece	IV(R)	×	NR	52 (104)	7	NR	✓	✓	×	✓

Study Country	Level of evidence[a] (P or R)	Manufacturer sponsored	Patient overlap	N (Ni)	Follow-up (years)	Losses to follow-up	Included for			
							Safety	Re-operation	Other effectiveness	Patient satisfaction
Revision reconstruction										
Hammond et al (2012) United States	IV (P)	✓	NR	68 (113)	6	At six years: 34%	✓	✓	✓	✓
Cunningham & McCue (2009) United States	IV (P)	✓	NR	60 (NR)	6	Non-compliance at six years 36%	✓	✓	×	✓
Maxwell et al (2012) United States	IV (P)	✓	NR	68 (112)	6	Non-compliance at six years 25%	✓	✓	✓	✓
PERMANENT EXPANDERS										
Primary reconstruction										
Cicchetti et al (2006) Italy	IV(P)	×	NR	NR (61)	5	NR	✓	✓	✓	×
Chew et al (2010) United Kingdom	IV(R)	×	NR	NR (68)	12.5	NR	✓	✓	×	✓
Gui et al (2008) United Kingdom	IV(P)	✓	NR	110 (127)	5.25	10.6% did not complete the questionnaire 20/107	×	×	×	✓
Revision reconstruction										
Cicchetti et al (2006) Italy	IV(P)	×	NR	NR (46)	5	NR	✓	✓	✓	×
Primary/revision not specified										
Goh et al (2010) United Kingdom	IV(R)	×	NR	NR (240)	5.4	NR	✓	✓	✓	×

N: number of patients; Ni: number of implants; NR: not reported; P: prospective study design; R: retrospective study design

[a] NHMRC levels of evidence (NHMRC 2000); Follow-up is mean except in cases noted with b

✓ yes; ×: no

FDA Allergan and Mentor studies (FDA 2011a)

The FDA update on the safety of silicone gel-filled implants reported the results of two studies which report safety data at eight and 10 years post-implantation. No peer reviewed publications of this data are available.

The study conducted by the manufacturer Allergan assessing the Inamed silicone breast implant (FDA 2011a) evaluated 44 primary reconstruction patients (initial cohort 98) at 10 years and reported on more safety outcomes than the six year data published in Spear et al (2007). The study (FDA 2011a) conducted by the manufacturer Mentor assessing MemoryGel silicone implants evaluated 151 patients for primary reconstruction at eight years post-implantation (initial cohort of 251 patients) and reported on more safety outcomes than the six year data published in Cunningham and McCue (2009). All results are provided as Kaplan-Meier cumulative incidence rates.

Critical appraisal of the peer reviewed literature

A summary of the checklist questions and results of the critical appraisal for the included studies (reconstructive indication) are presented in Table 10. Of the 14 included studies, 11 reported adverse events related to the procedure, including rupture, deflation and wrinkling or rippling, which were considered adverse events in this rapid review. Capsular contracture was predominantly defined using the Baker scale (7 of 11 studies which assessed capsular contracture). The Baker scale grades capsular contracture according to several characteristics including feel, appearance and pain with adverse capsular contracture defined as grades III and above (Wong et al 2006). Total patient numbers per study for the reconstructive indication ranged from 52 patients (Yiacoumettis 2005) to 572 (Hammond et al 2012).

Eight of the 14 included studies were conducted prospectively (Benediktsson and Perbeck 2006; Cicchetti et al 2006; Cunningham and McCue 2009; Gui et al 2008; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007; Walker et al 2009). The remaining six studies were retrospective case series evidence; and this makes it difficult to determine whether outcomes did not occur or were not reported; especially as a prospective design allows baseline measurement and ensures that patient selection criteria, treatment protocol used, and outcome measures are predefined and standardised (Moga et al 2012). Additionally, where raw data were reported it was unclear as to whether an intention-to-treat or per-protocol analysis was used. The description of implants used was clear in only nine studies (manufacturer and composition reported) and hence the sub-group analysis of adverse events according to manufacturer and indication for implantation was limited. Furthermore, only five studies clearly stated that patient enrolment was consecutive and reporting of prior or concurrent therapies in patients undergoing reconstruction was poor (five of 14 studies reporting prior/concurrent therapy). A subgroup analysis of adverse events according to prior therapy was complicated by a paucity of data.

Reporting and assessment of adverse events was variable, 11 of the 14 studies reported at least one outcome pertaining to implant rupture, deflation, capsular contracture or wrinkling and/or rippling. Magnetic resonance imaging (MRI) was considered the gold standard for the detection of defects in the shell wall of breast prostheses; as ultrasound and clinical examination or self-reporting does not detect silent rupture (either intracapsular; or extracapsular involving the leakage of silicone into

surrounding tissue). Also, MRI is able to quantify the extent of leakage (Juanpere et al 2011). The method of rupture assessment was MRI in only four included studies, and in three of the four, only a subset of patients were enrolled in an MRI sub-study. The method of patient selection for MRI sub-studies was not reported and so it is unclear as to whether the subset of patients selected appropriately represents the incidence of rupture in the study population. All patients assessed by MRI (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007) received silicone gel-filled breast implants. No reports of mammographic or ultrasound assessment of the breast implants were identified (Juanpere et al 2011). Of the eight studies that measured patient satisfaction, only one (Murphy et al 2009) used a validated tool, which was a modified version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire BR-23 (QLQ BR-23) Body Image Subscale (Sprangers et al 1996).

Results were generally reported as Kaplan-Meier estimates with 95 per cent confidence intervals at six years or more. The Kaplan-Meier estimates reported within the included studies represent the likelihood of experiencing the specified outcome at a given time point. The precision of the estimate depends on the number patients available for analysis at a given time point; interpretation of the results is, therefore, confounded by variable reporting of losses to follow-up at time points beyond the mean or median follow-up. Additionally, results were not reported uniformly across the studies and no one outcome was reported by all the included studies.

Estimates should be interpreted with caution as the Kaplan-Meier analysis assumes that the probability of the event depends only on time. This may not necessarily be the case; however, as the included studies invariably reported results as Kaplan-Meier estimates little can be inferred about the impact of other factors on outcomes of interest. Additionally, in the case of breast implantation the occurrence of many complications can be considered competing risks and hence the results may be overestimated.

Of the 14 studies identified, only four reported all outcomes related to safety and effectiveness; one in patients undergoing primary reconstruction with saline-filled implants and three in patients undergoing primary reconstruction with silicone gel-filled implants. Three of the included studies did not report safety outcomes. This information is summarised in Table 9.

Table 10 Critical appraisal summary of the peer reviewed studies, reconstructive indication

Critical appraisal				
Reconstruction, all implant types (n=14)				
Question	**Yes**	**No**	**Unsure/Partial**	**Not assessed**
Is the hypothesis/aim/objective of the study clearly stated?	14	0	0	0
Was the study conducted prospectively?	8	6	0	0
Were the cases collected in more than one centre?	6	8	0	0
Were participants recruited consecutively?	5	0	9	0
Are the characteristics of the participants included in the study described? (Reconstructive/augmentation; women)	14	0	0	0
Are the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	9	3	2	0
Did participants enter the study at a similar point in the disease?-	2	3	9	0
Was the implant of interest clearly described?	9	1	4	0
Was the surgical procedure clearly described?	7	5	2	0
Were additional interventions (co-interventions) clearly described (prior and concurrent treatments)?	5	9	0	0
Are all outcome measures established a priori?	11	3	0	0
Were the relevant outcomes assessed blinded to intervention status?-	0	5	9	0
Were the relevant outcomes measured with appropriate objective and/or subjective methods?	4	5	5	0
Method of rupture assessment (appropriate being surgical exploration or MRI)	1	3	3	7
Was a validated patient satisfaction tool used?	1	7	0	6
Was capsular contracture classified using the Baker scale and defined as grades III/IV?	7	1	3	3
Were the relevant outcomes (patient satisfaction) measured before and after the intervention?	1	13	0	0
Were raw data reported?	10	4	0	0
Was the nature of follow-up reported?	13	1	0	0
Was the loss to follow-up reported?	11	3	0	0
Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	6	7	1	0
Are the adverse events related to the intervention reported?	4	6	4	0
Are both competing interests and sources of support for the study reported?	7	4	3	0

Modified critical appraisal checklist (IHE 2012)
n: number of studies

Safety

Capsular contracture

Overall, safety outcomes amongst the included studies were poorly and variably reported with the most consistent reporting associated with capsular contracture. In the context of this review capsular contracture was defined as Baker's grade III or IV and where lower grades have been reported in the included studies, those results are reported separately. Capsular contracture is a common complication following breast implantation and correction of capsular contracture may require the surgical removal of the capsule by open capsulotomy and in some cases the removal and/or replacement of the implant. In addition, wrinkling and/or rippling of an implant in some cases can be an early indication of early capsular contracture.

Cancer incidence or recurrence of cancer

Although the development of cancer and recurrence of cancer have not been associated with breast implantation concern has been raised about the potential of breast implants to mask the detection of breast cancer. A Canadian study (Lavigne et al 2011; Pan et al 2012; Xie et al 2010), which compared incident cancers and vital status of 24,558 women who received bilateral cosmetic breast implants, and 15,893 women who underwent other plastic surgery procedures, suggested that breast implants may delay the detection of breast cancer; however, the study did not find a statistically significant difference in survival between the breast implant and other plastic surgery groups. The recurrence of cancer or incidence of cancer within the included studies has been reported in the results of the safety analysis; however, it should be noted that this does not imply a causal relationship between the breast prosthesis or implantation procedure and the recurrence or development of cancer.

Primary reconstruction, with saline-filled implants

Of the four studies using saline-filled implants three reported safety outcomes; and Benediktsson and Perbeck (2006) and Walker et al (2009) reported on multiple safety outcomes (Table 11). One study included for safety (Benediktsson and Perbeck 2006; Walker et al 2009) reported Kaplan-Meier estimates of capsular contracture. Capsular contracture was defined as Baker's grade III or IV unless otherwise reported. Levi et al (2008) only reported on rupture occurring in 43 of 516 implants.

Walker et al (2009) reported Kaplan-Meier estimates of complications at both five and 10 years follow-up. The results indicate that the risk of experiencing capsular contracture increases with the in situ duration of the implant. The study by Benediktsson and Perbeck (2006) reported that the majority of capsular contracture cases (15 of 22 cases) had occurred by one year. Ten patients in this study with capsular contracture had previously received radiation therapy, and 12 had not ($p=0.012$). Also, Kaplan-Meier estimates of wrinkling or rippling were reported by Walker et al (2009) at five years (24.6 %; 95% CI 18.6-30.6) and noted that the most common reasons for re-operation were capsular contracture and asymmetry. In addition, Benediktsson and Perbeck (2006) reported that over half of all patients who experienced capsular contracture underwent a subsequent re-operation.

Notably Walker et al (2009) reported high estimates of breast pain at both five and ten years (greater than 15%); breast pain can be associated with capsular contracture which was also high in this study. No definition of breast pain was provided.

Table 11 Safety in primary reconstruction with saline-filled implants

	Walker et al (2009)[a]	Walker et al (2009)[a]	Benediktsson & Perbeck (2006)
Follow-up (years)	5	10	5
Patients (implants)	237 (316)	237 (316)	107 (145)
Capsular contracture	35.7 (29.0-42.4)	51.7 (44.6-59.2)	22/107[b] (20.6%)
Breast pain	17.7 (12.4-23.0)	33.0 (26.4-40.7)	NR
Nipple hypersensitivity	0.4 (0.0-1.2)	NR	NR
Skin hypersensitivity	6.3 (2.9-9.6)	NR	NR
Loss of nipple sensation	18.1 (12.5-23.8)	NR	NR

Note: reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.
NR: not reported.
a outcomes occurring in <7% of patients were not reported.
b occurrences by 1 year (n=15), 2 years (n=3) and by 5 years (n=4).

Rupture

For three studies (Benediktsson and Perbeck 2006; Levi et al 2008; Walker et al 2009) incidences or Kaplan-Meier estimates of breast implant rupture for participants undergoing primary reconstruction with saline-filled implants are summarised in Table 12 (Benediktsson and Perbeck 2006; Levi et al 2008; Walker et al 2009).

In the study by Walker et al (2009) Kaplan-Meier estimates of deflation were available at both five and 10 years of follow-up. At five years, the Kaplan-Meier estimate was 7.5 per cent (95% CI 3.8-11.2) which increased to 22.5 per cent (95% CI 16.8-29.7) at ten years. The increase in the estimate of deflation from five to 10 years in Walker et al (2009) supports the idea that the risk of implant rupture or deflation increases over time.

Rates of deflation reported by Benediktsson and Perbeck (2006) and Levi et al (2008) were similar (17.2% and 16.0%). However, Benediktsson and Perbeck (2006) excluded from analysis patients who experienced implant failure prior to reaching two years of follow-up (n=14) and therefore this figure may underestimate the total rate of deflation across the study population.

Table 12 Rupture in primary reconstruction with saline-filled breast implants

Study	N (Ni)	Follow-up (years)	Rupture rate	
			n/N (%)	KM % (95% CI)
Benediktsson & Perbeck (2006)[a]	107 (145)	5	25/145[b] (17.2)	NR
Levi et al (2008)	NR (175)	6.04	28/175[b] (16.0)	NR
Walker et al (2009)	237 (316)	5	NR	7.5 (3.8-11.2)
Walker et al (2009)	237 (316)	10	NR	22.5 (16.8-29.7)

NR: not reported; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate; CI confidence interval.
a Five patients had their implants replaced; the study reported 25 incidents of deflation in 11 patients.
b Calculated based on number of implants.

Capsular contracture sub-group analyses according to manufacturer

Benediktsson and Perbeck (2006) report capsular contracture according to patients undergoing implantation with either the McGhan microcell implant (n=45) or the Mentor Siltex (n=62) implant with and without radiotherapy. Both are textured implants and the results are summarised in Table 13. A higher proportion of patients implanted with the McGhan prosthesis experienced capsular contracture (p=0.025) and treatment with prior radiotherapy was associated with a higher

proportion of patients experiencing capsular contracture regardless of implant (p=0.012). No other outcomes were analysed according to manufacturer.

Table 13 Capsular contracture, implant manufacturer and prior therapy in Benediktsson and Perbeck (2006)

	McGhan			Mentor		
	Prior radiation	No prior radiation	Total	Prior radiation	No prior radiation	Total
Capsular contracture n/N (%)	6/11 (54.5)	8/34 (23.5)	14/45 (31.1)	4/13 (30.8)	4/49 (8.2)	8/62 (12.9)

N: number of patients; n: number of events.

Primary and revision reconstruction with silicone gel-filled implants

Primary reconstruction

Six studies (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007; Tarantino et al 2006; Yiacoumettis 2005) reported safety data in patients undergoing primary reconstruction with silicone gel-filled breast implants. Follow up periods ranged from six to 14.9 years. The results are reported as Kaplan-Meier estimates in four of the studies and as raw incidences in two. Infection was the most frequently reported outcome (reported by five of six studies) followed by capsular contracture (reported by four studies) and breast pain. The results are summarised in Table 14.

Capsular contracture was reported as a Kaplan-Meier estimate in all instances and the range in estimates was large (3.1% to 15.9%); confidence intervals also tended to be large indicating relative uncertainty in the results. Hammond et al (2012) reported Grade II capsular contracture requiring surgical intervention as a Kaplan-Meier estimate of 4.2 per cent (95%CI 2.0-8.7). Capsular contracture was a common reason for reintervention in all of the studies (greater than 10 per cent except Hammond et al). One study (Tarantino et al 2006) reported capsular contracture as having occurred in 16 per cent of patients but no further details are provided.

Four of the five studies estimating implant rupture also reported estimates of wrinkling and/or rippling (Hammond et al 2012; Maxwell et al 2012; Spear et al 2007) and results are summarised in Table 14. Hammond et al (2012, Maxwell et al (2012 and Spear et al (2007) all report estimates at six-year follow-up whilst Spear et al (2007) also reported 10-year estimates in the FDA study. Spear et al (2007) reported the highest estimate of wrinkling or rippling at six-year follow-up, at greater than 10 per cent, with a large confidence interval. This may be due to the small number of study participants (98 patients).Table 14 Safety in primary reconstruction with silicone-filled implants

	Hammond et al (2012)[a]	Spear et al (2007)[b]	Cunningham & McCue (2009)[c]	Maxwell et al (2012)[d]	Yiacoumettis (2005)	Tarantino et al (2006)
Follow-up (years)	6	6	6	6	7	14.9
Patients (implants)	191 (328)	98 (127)	251 (NR)	225 (351)	52 (104)	68 (NR)
Capsular contracture	10.1 (6.2-16.0)[e]	15.9 (9.7-25.6)[f]	13.7 (9.7-19.1)[g]	3.1 (1.4-6.9)[h]	NR	NR (16%)
Grade II capsular contracture	4.2 (2.0-8.7)	NR	NR	NR	NR	NR
Wrinkling &/or rippling	4.0 (1.9-8.2)	10.2 (5.1-19.5)	NR	3.1 (1.4-6.9)	NR	NR
Infection	1.6 (0.5-5.0)	NR	6.1 (3.7-10.0)	4.8 (2.6-8.7)	0/52 (0%)[i]	1/68 (1.5%)[i]
Haematoma	NR[j]	NR	NR	1.0 (0.3-4.0)	0/52 (0%)[i]	NR
Breast pain	2.8 (1.2-6.6)	3.1 (1.0-9.3)	NR	4.2 (2.1-8.2)	NR	NR
Seroma	3.4 (1.5-7.4)	NR	NR	1.4 (0.5-4.3)	NR	NR
Necrosis	NR	NR	NR	NR	7/52 (13.5%)[i,l,k]	NR
Swelling	NR[j]	7.1 (3.5-14.4)	NR	3.8 (1.9-7.5)	NR	NR
Wound dehiscence	NR[j]	NR	NR	NR	0/52 (0%)[i,l]	NR
Delayed wound healing	1.0 (0.3-4.1)	NR	NR	0.5 (0.1-3.3)	NR	NR
Cancer recurrence	2.5 (0.9-6.5)	NR	NR	NR	NR	1/68 (1.5%)[i]
Tenderness/soreness	1.4 (0.3-5.7)	NR	NR	NR	NR	NR
Redness	NR	NR	NR	0.9 (0.2-3.7)	NR	NR
Mass/cyst	4.6 (2.2-9.8)	NR	NR	NR	NR	NR
Nipple sensation changes	2.9 (1.2-6.9)	NR	NR	NR	NR	NR
Breast sensation changes	1.1 (0.3-4.5)	NR	NR	NR	NR	NR
Inflammation/irritation	2.1 (0.8-5.6)	NR	NR	NR	NR	NR
Skin lesion	1.8 (0.6-5.5)	NR	NR	NR	NR	NR
Suture complication	1.7 (0.6-5.3)	NR	NR	NR	NR	NR
New diagnosis of rheumatic disease	3/191 (1.6%)[m] 1.7 (0.6-5.1)	NR	NR	NR	NR	NR
Metastatic disease	2.3 (0.9-5.9)	NR	NR	NR	NR	NR
Death - metastatic disease	1.4 (0.4-5.5)	NR	NR	NR	NR	NR
Erythema	NR[j]	NR	NR	NR	NR	NR
Muscle atrophy	NR[j]	NR	NR	NR	NR	NR
Paraesthesia	NR[j]	NR	NR	NR	NR	NR

Note: Results are Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted. NR: not reported.
a Outcomes occurring in <1% of patients were not reported by the study authors.
b Outcomes occurring in <5% of patients were not reported by the study authors.
c Outcomes occurring in <10% of patients were not reported by the study authors.
d Outcomes occurring in <2% of patients were not reported by the study authors.
e Capsular contracture accounted for less than 10% of any re-operation in this cohort.
f Capsular contracture was the reason for re-operation in 14.5% of all re-operations and in 21.2% of implant removals with or without replacement.
g Of 105 re-operations in 82 women in Reconstruction cohort, reason for re-operation was capsular contracture II/III/IV (16.2%) of cases.
h Capsular contracture accounted for 12.9% of any re-operation and 16.1% of implant removals (with or without replacement).
i n/N (%); N:number of patients; n: number of events.
j authors reported this may have occurred in less than 1% of patients.
k Full (n=1) or partial (n=4) necrosis of the NAC and flap necrosis that spontaneously healed (n=2).
l Wound dehiscence with implant exposure.
m Three new diagnoses of rheumatic disease in three primary reconstruction patients: rheumatoid arthritis (10 months), other inflammatory arthritis (11 months), and other mechanical/degenerative condition (16 months).

Primary reconstruction (FDA 2011a)

Estimates of capsular contracture at eight and 10 years in both studies reported in the FDA update (FDA 2011a) indicated that capsular contracture was a frequent complication; the lower boundary of

the confidence interval was above 10 per cent in both instances. Losses to follow-up in both studies were substantial and in the study by Allergan over half of the included patients were lost to follow-up. This is reflected in the large confidence intervals and thereby low precision of the estimates reported in Table 15.

A Kaplan-Meier estimate for wrinkling and/or rippling was only provided in the study conducted by Allergan and was estimated at 10.2 per cent (95% CI 5.2-19.6) at 10-year follow-up (FDA 2011a). No estimation of wrinkling and/or rippling was calculated in the study by Mentor (FDA 2011a).

Table 15 Data from the FDA update, primary reconstruction with silicone gel-filled implants (FDA 2011a)

	Allergan	Mentor
Length of follow-up, years	10	8
Number of patients	98	251
Losses to follow-up, n (%)	54 (55.1)	100 (39.8)
Capsular contracture (Baker II)	NR	4.4 (2.3-8.3)
Capsular contracture (Baker III/IV)	24.6 (16.2-36.2)	15.3 (11.1-20.9)
Wrinkling and/or rippling	10.2 (5.2-19.6)	NR
Breast mass	NR	5.2 (2.9-9.3)
Breast pain	6.8 (2.8-16.1)	2.8 (1.2-6.2)
Breast/skin sensation changes	0	0
Bruising	1.0 (0.1-7.1)	NR
Delayed wound healing	1.0 (0.1-7.2)	0
Granuloma	NR	0
Haematoma	1.5 (0.2-10.4)	NR
Infection	3.2 (1.0-9.5)	6.2 (3.8-10.2)
Irritation	0	NR
Inflammation of breast	NR	0
Lactation difficulties	NR	0
Metastatic disease	NR	5.7 (3.3-9.6)
Miscarriage	NR	2.3 (1.0-5.6)
New diagnosis of breast cancer	NR	1.9 (0.7-5.1)
Necrosis	2.3 (0.6-8.8)	NR
New diagnosis of rheumatic disease	NR	2.6 (1.1-6.2)
Nipple complications	3.3 (1.1-9.8)	1.3(0.4-4.1)
Nipple sensation changes	NR	2.1 (0.9-5.0)
Pre-eclampsia at 36 weeks pregnant	NR	0
Redness	2.1 (0.5-8.3)	NR
Seroma	2.4 (0.3-15.7)	4.8 (2.8-8.4)
Skin rash	2.1 (0.5-7.9)	NR
Swelling	7.1 (3.5-14.4)	NR

Note: all results presented as Kaplan-Meier estimates % (95% confidence interval); f/u: follow-up; n: number of patients

Rupture

Five studies (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007; Tarantino et al 2006) reported implant rupture in patients undergoing primary reconstruction with silicone gel-filled breast implants. All results are summarised in Table 16.

All studies except for Tarantino et al (2006) reported rupture as a Kaplan-Meier estimate via conducting an MRI study on a subset of study participants; however Hammond et al (2012) also reported incidence of rupture at six years. At 15 years Tarantino et al (2006) reported rupture in two of 68 (2.9%) patients, which is lower than the majority of Kaplan-Meier estimates reported by other studies at between six and 10-year follow-up. However the authors assessed rupture based on general symptoms including dizziness, swelling of extremities and generalised pruritus. The incidence reported may be an underestimate of implant rupture had MRI studies been conducted, which may have detected instances of silent rupture. Kaplan-Meier estimates of rupture at six years were reported in four of the five studies and had a range of 1.5 to 9.3 per cent at six years. Spear et al (2007) reported the highest estimate of rupture at 9.3 per cent (95% CI 3.6-22.9). The lowest Kaplan-Meier estimate of rupture was 1.5 per cent (95% CI 0.2-11.1) reported by Hammond et al (2012). Estimates reported by Maxwell et al (2012) and Spear et al (2007) were noticeably less precise, reasons for this are unclear but may be related to small sample-sizes.

Rupture (FDA 2011a)

In both the Allergan and Mentor cohorts (FDA 2011a) rupture was estimated via conducting an MRI study on a subset of participants and in both cases the cumulative incidence of rupture reported at eight or 10 years was over twice as high as the six-year reports.

Results must be interpreted carefully as confidence intervals are relatively large and losses to follow-up at eight and 10 years in both studies were significant (54/98 (55%) patients in the Allergan study and 100/251(40%) in the Mentor study). Additionally, the initial MRI cohorts used to determine rupture rates were small (Allergan: 50, Mentor: 134; losses to follow-up unknown).

Table 16 Rupture in primary reconstruction with silicone gel-filled implants

			Rupture rate	
Study	**N (Ni)**	**Follow-up (years)**	**n/N (%)**	**KM % (95% CI)**
Hammond et al (2012)	191 (328)	6	2/191 (1.1%)	1.5 (0.2-11.1)[a]
Spear et al (2007)	98 (127)	6	NR	9.3 (3.6-22.9)[a]
Cunningham & McCue (2009)	251 (NR)	6	NR	3.8 (1.4-9.8)[a]
Maxwell et al (2012)	225 (351)	6	NR	7.5 (3.2-17.2)[a]
Tarantino et al (2006)	68 (NR)	14.9	2/68[b] (2.9%)	NR
Data from the FDA update (FDA 2011a)				
Allergan	98 (NR)	10[d]	NR	27.2 (17.3-41.3)
Mentor	251 (NR)	8[e]	NR	14.0 (7.6-25.0)

NR: not reported; N: number of patients; Ni: number of implants; n/N number of incidents/ number of patients unless otherwise specified; CI confidence interval; KM: Kaplan-Meier estimate.
a Estimates based on MRI sub-study.
b Implant rupture diagnosed based on general symptoms including dizziness, swelling of extremities and generalised pruritus.
d At 10 years 54 patients had been lost to follow-up.
e At 8 years 100 patients had been lost to follow-up.

Rupture subgroup analyses according to manufacturer

In patients undergoing primary reconstruction with silicone gel-filled implants, four studies reported the manufacturer of the implant used (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007), as described in Table 18. Two studies utilised implants manufactured by Mentor (Cunningham and McCue 2009; Hammond et al 2012) and two utilised implants manufactured by Allergan (Maxwell et al 2012; Spear et al 2007). Overall the Kaplan-Meier estimates of rupture had overlapping confidence intervals so no conclusions can be drawn. The estimates provided by studies using Allergan implants were notably less precise. This may be attributable to the smaller number of enrolled patients in the Allergan studies as compared to the Mentor cohorts. In both instances a large number of patients were lost to follow-up and thus censored from the estimates. The smaller initial patient numbers in the Allergan studies may have compounded the effect of limited retention rates and resulted in imprecise estimates.

Table 17 Rupture reported according to implant manufacturer in primary reconstruction

	Allergan		Mentor	
	Spear et al (2007)	**Maxwell et al (2012)**	**Hammond et al (2012)**	**Cunningham & McCue (2009)**
Rupture rate n/N (%)	NR	NR	2/191 (1.1%)	NR
Rupture rate KM % (95% CI)	9.3 (3.6-22.9)[a]	7.5 (3.2-17.2)[a]	1.5 (0.2-11.1)[a]	3.8 (1.4-9.8)[a]

CI confidence interval; NR: not reported; N: number of patients; n: number of events; KM: Kaplan-Meier estimate.
a Estimates based on MRI sub study.

Rupture subgroup analyses according to manufacturer (FDA 2011a)

Estimates of capsular contracture at eight and 10 years in both studies indicated that capsular contracture was a frequent complication; the lower boundary of the confidence interval was above 10 per cent in both instances. Implant wrinkling and/or rippling was reported in the study by Allergan only and was estimated at 10.2 per cent (95% CI 5.2-19.6) which is similar to the Kaplan-Meier estimate reported at six-year follow-up (10.2% 95% CI 5.1-19.5). Losses to follow-up in both studies were substantial and in the study by Allergan over half of the included patients were lost to follow-up. This is reflected in the precision of the estimates reported in Table 15.

Revision reconstruction

Three studies (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012) report safety data for patients undergoing revision reconstruction with silicone gel-filled breast implants. All studies had a follow-up period of six years. Capsular contracture, infection, haematoma, breast pain, swelling and seroma were the most frequently reported outcomes (reported by at least two studies) and are summarised in Table 18. Capsular contracture was reported by all three studies and had a range of estimates between 16.4 per cent and 25.2 per cent. All estimates had relatively large confidence intervals which may be due in part to the small number of study participants (range 60 to 68 patients). In all three studies capsular contracture was a common reason for re-operation accounting for greater than 10 per cent of any re-operation in all studies.

Table 18 Safety in revision reconstruction with silicone gel-filled implants

	Hammond et al (2012)	Cunningham & McCue (2009)	Maxwell et al (2012)
Follow-up, years	6	6	6
Patients (implants)	68 (113)	60 (NR)	68 (112)
Capsular contracture	16.4 (8.7-29.8)[b]	25.2 (15.7-38.9)[c]	18.3 (10.5-30.8)[d]
Wrinkling and/or rippling	12.2 (5.9-24.5)	NR	7.7 (3.3-17.4)
Infection	3.0 (0.8-11.4)	0 (0)	4.5(1.5-13.3)
Haematoma	1.5 (0.2-10.0)	NR	0 (0)
Breast pain	3.3 (0.8-12.8)	NR	4.8 (1.6-14.3)
Seroma	4.6 (1.5-13.5)	NR	6.2 (2.4-15.8)
Necrosis	NR[a]	NR	NR
Swelling	1.5 (0.2-10.0)	NR	3.2 (0.8-12.4)
Wound dehiscence	NR[a]	NR	NR
Delayed wound healing	NR[a]	NR	2.9 (0.7-11.3)
Cancer recurrence	3.6 (0.9-13.9)	NR	NR
Tenderness/soreness	NR[a]	NR	NR
Redness	NR	NR	5.1 (1.6-15.3)
Mass/cyst	NR[a]	NR	NR
Nipple sensation changes	NR[a]	NR	NR
Breast sensation changes	NR[a]	NR	NR
Inflammation/irritation	3.0 (0.8-11.3)	NR	NR
Skin lesion	4.3 (1.1-16.3)	NR	NR
Suture complication	NR[a]	NR	NR
New diagnosis of rheumatic disease	NR[a]	NR	NR
Metastatic disease	1.6 (0.2-10.9)	NR	NR
Death - metastatic disease	NR[a]	NR	NR
Erythema	1.5 (0.2-10.0)	NR	NR
Muscle atrophy	1.5 (0.2-10.1)	NR	NR
Paraesthesia	3.4 (0.9-12.9)	NR	NR

Note: reported as Kaplan-Meier estimates (95% confidence intervals) unless otherwise denoted
NR: not reported
a May have occurred in less than 1% of patients, Hammond et al (2012) did not report events occurring in <1% of patients.
b Capsular contracture accounted for greater than 10% of any re-operation.
c Capsular contracture accounted for 22.2% of any re-operation (occurring in > 8% of re-operation cases).
d Capsular contracture accounted for 14.7% of any re-operation.

Revision reconstruction (FDA 2011a)

The Allergan study evaluated eight revision reconstruction patients (initial cohort 15) at 10 years and the Mentor study evaluated 36 revision reconstruction patients (initial cohort 60) at eight years (FDA 2011a). All results are provided as Kaplan-Meier cumulative incidence rates and are detailed in Table 20.

Capsular contracture, wrinkling and/or rippling, bruising, seroma/fluid accumulation and skin rash were reported in the study by Allergan. Capsular contracture, bruising, seroma/fluid accumulation and skin rash all had a cumulative incidence rate of 6.7 per cent (95% CI 0.2-31.9). The confidence interval associated with these estimates indicates a substantial amount of uncertainty in the results. This may be due to the small sample size and large losses to follow up; only eight of 15 patients were evaluated at 10 years. Wrinkling was also reported and had a cumulative incidence of 0 at 10 years (0/8 in patients evaluated at 10 years).

The study by Mentor reported more safety outcomes than the study by Allergan (FDA 2011a). The estimated rate of capsular contracture was 6.7 per cent (95% CI 0.2-31.9) in the study by Allergan and 23.1 per cent (95% CI 14.1-36.6) in the study by Mentor; however, it is difficult to draw a meaningful comparison of these estimates as the boundaries of the confidence intervals overlap limiting the ability to determine whether these findings are statistically significant. In addition, the estimates reported in the study by Allergan are less precise relative to the Mentor core study.

Rupture

Three of the studies which used silicone gel-filled breast implants for breast reconstruction reported outcomes for both primary and revision reconstruction (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012). In all studies rupture estimates were based on results for patients enrolled in an MRI sub-study. Kaplan-Meier estimates of rupture had a range of 0 to 14.3 per cent at six years and were imprecise indicated by the large confidence intervals (Hammond et al 2012 and Maxwell et al 2012, respectively). The small number of study participants is likely to have contributed to imprecision in the estimates reported below (Table 19).

Table 19 Rupture in revision reconstruction with silicone gel-filled implants

Study	N (Ni)	Follow-up (years)	Rupture rate	
			n/N (%)	KM % (95% CI)
Hammond et al (2012)	68 (113)	6	0	0[e]
Cunningham & McCue (2009)	60 (NR)	6	NR	5.9 (0.9-35.0)[a,b]
Maxwell et al (2012)	68 (112)	6	NR	14.3 (4.8-38.0)[a]

NR: not reported; N: number of patients; Ni: number of implants; n: number of events; CI confidence interval; KM: Kaplan-Meier estimate.
a Estimates based on MRI sub study.
b Suspected or confirmed.

Rupture (FDA 2011a)

The cumulative incidence of rupture in the Allergan study was 6.7 per cent (95% CI 0.2-31.9) at ten years and 21.3 per cent (95% CI 7.3-53.3) in the Mentor study at eight years. Six-year rupture data were not available from Spear et al (2007) and eight-year data in the Mentor study suggested a much higher estimate of rupture at eight years as compared to six (Cunningham and McCue 2009). In both cases, rupture was estimated by conducting an MRI sub-study of participants (five patients in the Allergan study and 28 in the Mentor study) and losses to follow-up within those cohorts were unknown. The limited patient data is reflected in the imprecision of the results.

Rupture sub-group analyses according to manufacturer

In patients undergoing revision reconstruction with silicone gel-filled implants two studies reported the results of implant manufactured by Mentor (Cunningham and McCue 2009; Hammond et al 2012) and one by Allergan (Maxwell et al 2012). The Kaplan-Meier estimate of rupture was higher in the study which used Allergan implants than in either of the two studies involving Mentor implants; however, the Kaplan-Meier estimates for the Allergan implants was calculated at 10-year follow-up whilst the two studies assessing Mentor implants only estimated rupture at eight-year follow-up.

Table 20 Data from the FDA update, revision reconstruction with silicone gel-filled implants (FDA 2011a)

	Allergan	Mentor
Length of follow-up, years	10	8
Number of patients	15	60
Losses to follow-up, n (%)	7 (46.7)	24 (40)
Capsular contracture (Baker II)	NR	4.0 (1.0-15.2)
Capsular contracture (Baker III/IV)	6.7 (0.2-31.9)	23.1 (14.1-36.6)
Wrinkling and/or rippling	0[a]	NR
Breast mass	NR	7.2 (2.8-18.2)
Breast pain	0	5.2 (1.7-15.3)
Breast/skin sensation changes	0	1.8 (0.3-12.0)
Bruising	6.7 (0.2-31.9)	NR
Delayed wound healing	0	1.7 (0.2-11.3)
Granuloma	NR	2.4 (0.8-7.4)
Haematoma	0	NR
Infection	0	0
Irritation	0	NR
Inflammation of breast	NR	1.7 (0.2-11.4)
Lactation difficulties	NR	0
Metastatic disease	NR	4.0 (1.0-15.2)
Miscarriage	NR	0
New diagnosis of breast cancer	NR	1.7 (0.2-11.4)
Necrosis	0	NR
New diagnosis of rheumatic disease	NR	3.4 (0.9-12.9)
Nipple complications	0	0
Nipple sensation changes	NR	1.7 (0.2-11.3)
Pre-eclampsia at 36 weeks pregnant	NR	0
Redness	0	NR
Seroma	6.7 (0.2-31.9)	1.7 (0.2-11.3)
Skin rash	6.7 (0.2-31.9)	NR
Swelling	0	NR

f/u: follow-up; n: number of patients; all results are presented as Kaplan-Meier estimates % with 95% confidence intervals. a cumulative estimate of 0% as none of the eight patients were evaluated at 10-year follow-up.

Primary and revision reconstruction with permanent expanders

Three studies (Chew et al 2010; Cicchetti et al 2006; Goh et al 2012) report safety data in patients who received permanent expanders. One study (Cicchetti et al 2006) reported outcomes for both primary and reconstructive patients. The longest follow-up period associated with reporting of adverse events was 5.4 years. Although Chew et al (2010) reported a follow-up period of 12.5 years, the only adverse events reported were those associated with implant removal at five years.

All three studies reported the incidence of capsular contracture and wrinkling and/or rippling Table 21. The incidence of capsular contracture was greater than 15 per cent and the incidence of wrinkling and/or rippling ranged from 4.4 to 14.2 per cent at five year or more of follow-up.

Infection was the only other outcome reported for all patients undergoing primary reconstruction and occurred in 5.8 per cent of patients (14/240) in Goh et al (2012), in 9.8 per cent of patients (6/61) in Cicchetti et al (2006) and in 16.2 per cent of implants (11/68) in Chew et al (2010) which only reported adverse events requiring implant removal. Other safety outcomes are summarised in Table 21.

Concurrent treatments

The incidence of capsular contracture was generally found to be higher in those patients who received prior or concurrent oncological treatment as compared to no treatment. Goh et al (2012) reported a significant difference between the patients who received prior therapy (postoperative radiotherapy) and those who did not ($p<0.0001$); capsular contracture occurred in 52 per cent (13/25) patients who received prior treatment as compared to 21.5 per cent (38/177) of patients who did not. Cicchetti et al (2006) did not conduct a test for statistical significance but reported that 32.4 per cent of implants (12/37) in patients who underwent prior therapy (neoadjuvant or adjuvant radiation alone or in association with chemotherapy) were associated with capsular contracture as compared to 22.2 per cent of implants (2/9) in patients who did not undergo prior therapy.

Revision reconstruction

Cicchetti et al (2006) reported results in 44 patients undergoing revision reconstruction and reported that capsular contracture occurred in 17.4 per cent of implants (8/46) and that wrinkling or rippling occurred in 4.3 per cent of implants (2/46).

Table 21 Safety in primary or revision reconstruction with permanent expanders

	Primary reconstruction			Revision reconstruction
	Chew et al (2010)	**Goh et al (2012)[a]**	**Cicchetti et al (2006)**	**Cicchetti et al (2006)**
Follow-up (years)	12.5	5.4	5	5
Patients (implants)	NR (68)	240 (256)	NR (61)	NR (46)
Capsular contracture	12/68[b,c,d] (17.6%)	51/240 (21.2%)	14/61 (23.0%)	NR
Wrinkling &/or rippling	3/68[b,i] (4.4)	34/240[b] (14.2)	5/61[b] (8.2)	5/61[b] (8.2)
Infection	11/68 (16.2%)[b,c]	14/240 (5.8%)	6/61 (9.8%)[b]	2/46 (4.3%)[b]
Haematoma	NR	NR (2.5%)	8/61 (13.1%) [b,e]	2/46 (4.3%)[b,g]
Breast pain	NR	29/240 (12.1%)	NR	NR
Necrosis	4/68 (5.9%)[b,c]	NR (5%)[f]	NR	NR
Extrusion	NR	NR (0.8%)	3/61 (4.9%)[b]	0/46 (0%)[b]
Injection port complications	NR	9/240 (3.8%)[h]	7/61 (11.5%)[b]	1/46 (2.2%)[b,g]
Granuloma	NR	0/240 (0%)	NR	NR

Note: reported as proportions of patients (n/N, %).
NR: not reported.
a Results include 16 patients undergoing implant replacement.
b Calculated based on number of implants.
c Only reported adverse event that required implant removal.
d Baker's definition of capsular contracture not reported.
e Included haematoma and seroma.
f Necrosis that required debridement.
g Included: Filler tube kinking (n=2), leakage from injection dome (n=1), rotation of the injection port(n=2), injection port infection(n=2) and filler tube fracture (n=2).
h Included: port/valve malfunction.
i includes only wrinkling leading to implant removal at five years.

Rupture

Three studies reported rupture amongst primary reconstruction patients who underwent implantation with permanent expanders (Chew et al 2010; Cicchetti et al 2006; Goh et al 2012). Cicchetti et al (2006) did not report rupture in revision reconstruction patients. Results are summarised in Table 22. Due to the retrospective study design of Chew et al (2010) and Goh et al (2012) and the lack of detail in the reporting of rupture it was difficult to ascertain whether rupture occurred but was not reported or did not occur within the included studies.

Gui et al (2008) reported that seven of 178 patients (3.9%) experienced implant loss. These results were excluded from Table 23 as no details regarding the nature of implant loss were provided. Chew et al (2010) reported three cases of implant leakage and/or failure as a reason for explantation of Becker expanders at five years. It was unclear whether incidence of rupture beyond five years was reported (total follow up 12.5 years). Goh et al (2012) reported no cases of "symptomatic rupture" amongst 240 patients in 5.4 years of follow-up.

Table 22 Rupture in primary reconstruction with permanent expanders

Study	N (Ni)	Follow-up (years)	Rupture rate	
			n/N (%)	KM % (95% CI)
Primary reconstruction				
Cicchetti et al (2006)[a]	NR (61)	5	NR	NR
Goh et al (2012)[a]	NR (240)	5.4	0/240[b,c] (0)	NR
Chew et al (2010)[a]	NR (68)	12.5	3/68[d] (4.4)	NR

NR: not reported; N: number of patients; Ni: number of implants: n: number of events; CI confidence interval; KM: Kaplan-Meier estimate.
a Studies include patients who have undergone prior or concurrent chemotherapy and/or radiotherapy treatment.
b Calculated based on number of implants.
c Symptomatic rupture only.
d This includes only implants which were removed by five years due to implant leak/failure.
e includes only wrinkling leading to implant removal at five years.

Rupture sub-group analyses according to manufacturer

The studies by Goh et al (2012) and Chew et al (2010) utilised expanders manufactured by Mentor and the study by Cicchetti et al (2006) utilised expanders manufactured by Allergan. There were insufficient data to conduct any analysis.

Effectiveness

Outcomes reported by authors assessing the effectiveness of saline-filled and silicone gel-filled breast implants include the incidence or Kaplan-Meier estimate of re-operation rate, reasons for re-operation, patient satisfaction or other effectiveness outcomes such as implant visibility, palpability and malposition.

Primary reconstruction with saline-filled implants

Re-operation

Three studies (Benediktsson and Perbeck 2006; Le et al 2005; Walker et al 2009) report the incidence or Kaplan-Meier estimate of re-operation, replacement or removal of the prosthesis for patients undergoing primary breast reconstruction with saline-filled implants. Walker et al (2009) reported Kaplan-Meier estimates at both five and 10 years post-implantation (Table 23) and the results suggest that the risk of total re-operation increases with time. Across all studies re-operation for any reason was common and implants were replaced in approximately half of all patients undergoing re-operation.

The total number of re-operations for definitive removal of the prosthesis in Benediktsson and Perbeck (2006) was unclear. The authors reported the incidence of re-operation related only to capsular contracture and rupture therefore it is unclear if re-operation was performed for any other reason during the study period. Fourteen patients had their implants replaced due to capsular contracture (n=9) or rupture (n=5).

Le et al (2005) also reported incidence data for 314 patients who received double-lumen implants for primary or revision reconstruction; of those patients, 98 (31.2%) underwent re-operation 77 of whom had their implant(s) replaced.

Table 23 Re-operation in primary reconstruction with saline-filled implants

Study (year)	N(Ni)	Follow-up (years)	Total re-operation n/N (%)	Implants replaced n/N (%)	Total re-operation KM % (95% CI)	Removal or replacement only KM % (95% CI)
Walker et al (2009)	237 (316)	5	NR	NR	44.5 (37.9-51.0)	28.0 (22.1-34.0)[a]
	237 (316)	10	NR	NR	54.6 (48.1-61.5)	39.5 (33.3-46.5)
Le et al (2005)[b]	149	12.4	72/149 (48.3)[c]	62/149 (41.6)	NR	NR
Le et al (2005)	314	12.4	98/314 (31.2)	77/314 (24.5)	NR	NR
Benediktsson & Perbeck (2006)	107 (145)	5	27/107 (25.3)	14/27 (51.9)	NR	NR

N: number of patients; Ni: number of implants; n: number of procedures; CI: confidence interval; NR: not reported; KM: Kaplan-Meier estimate.
a At least 70 patients had their implants removed (with or without replacement).
b Le reported 48 of the 1018 women with implants had prior radiotherapy; the number of women undergoing radiotherapy included in the analysis is unknown.
c Includes only explantation.

Reasons for re-operation

Walker et al (2009) reported that the most common reasons for any re-operation were capsular contracture and asymmetry. For patients who had their implants removed or replaced the most frequent reasons included capsular contracture (31.4%) or patient choice for style or size change

(21.4%). At least 14 of the 27 patients who underwent re-operation reported in the study by Benediktsson and Perbeck (2006) had their implants replaced due to rupture (n=5) or capsular contracture (n=9). Overall, total re-operation rates at five years or more across all included studies were greater than 25 per cent.

Other effectiveness

Walker et al (2009) was the only study to report any other effectiveness outcomes and results were available at five years only. The authors reported Kaplan-Meier estimates of implant palpability and visibility as well as implant malposition. Both estimates showed these outcomes occurring in greater than 15 per cent of patients at five years. The Kaplan-Meier estimate of implant palpability and visibility at five years was 27.1 per cent (95% CI 20.6-33.5) and the estimate of implant malposition was 16.9 per cent (95% CI 11.7-22.2).

Patient satisfaction

Walker et al (2009) used a survey to determine reasons for re-operation five and 10 years after breast implantation in a study of 1,138 patients who either underwent breast augmentation (901 women) or breast reconstruction (237 women) using Natrelle saline-filled implants (Allergan Pty Ltd.). At five years post-implantation 21.4 per cent of 70 explants in the breast reconstruction group were reoperated on due to patient request owing to their dissatisfaction with either implant style or size. Similar figures were reported at 10 years with 25 per cent of 104 explants in the reconstructive group resulting in revision due to requests by patients as a result of dissatisfaction with either implant style or size.

Primary reconstruction with silicone gel-filled breast implants

Seven studies reported effectiveness outcomes for primary reconstruction with silicone gel-filled breast implants (Cunningham and McCue 2009; Hammond et al 2012; Le et al 2005; Maxwell et al 2012; Spear et al 2007; Tarantino et al 2006; Yiacoumettis 2005).

Re-operation

Seven studies (Cunningham and McCue 2009; Hammond et al 2012; Le et al 2005; Maxwell et al 2012; Spear et al 2007; Tarantino et al 2006; Yiacoumettis 2005) reported re-operation (Table 24). The incidence of any type of re-operation was reported in four studies and ranged from 1.9 to 50 per cent (Cunningham and McCue 2009; Maxwell et al 2012; Tarantino et al 2006; Yiacoumettis 2005). Four studies reported Kaplan-Meier estimates for re-operation which ranged from 33.9 to 51.9 per cent at six-year follow-up.

Tarantino et al (2006) reported the highest incidence of re-operation, namely 50 per cent, and had the longest follow-up duration of 14.9 years. Conversely, the incidence of explantation in this study was the lowest at 10.3 per cent. The two other studies reporting the incidence of explantation recorded 16.3 and 26.7 per cent respectively (Cunningham and McCue 2009; Le et al 2005). Four studies reported the incidence of explantation at six-year follow-up which ranged from 10.3 to 36 per cent. Four studies reported Kaplan-Meier estimates of explantation at six years which ranged from 4.6 to 21.8 per cent; and these calculated estimates are significantly lower than the incidence of explantation at six-year follow-up. Three studies reported implant replacement as Kaplan-Meier estimates which ranged from 10.4 to 23.7 per cent.

Table 24 Re-operation in primary reconstruction with silicone gel-filled implants

Author (year)	N(Ni)	Follow-up (years)	Total re-operation n/N (%)	Explanted[a] n/N (%)	Total re-operation KM % (95%CI)	Explantation KM % (95%CI)	Replacement KM % (95%CI)
Cunningham & McCue (2009)	251 (NR)	6	82/251 (32.7)	41/251 (16.3)[a]	33.9 (28.3-40.3)	8.0 (5.1-12.4)	10.4 (7.1-15.3)
Maxwell (2012)	225 (351)	6	124/225[a] (55)	81/225[b] (36)	43.1 (36.7-50.0)	4.6 (2.4-8.7)	23.7 (18.3-30.2)
Le et al (2005)	333	12.4	NR	89/333 (26.7)[c]	NR	NR	NR
Hammond et al (2012)[d]	191 (328)	6	NR	NR	44.5 (37.5-52.2)	21.8 (16.4-28.7)[c]	NR
Spear et al (2007)	98 (127)	6	NR	NR	51.9 (42.0-62.6)	7.7 (3.5-16.4)	22.3 (14.9-32.5)
Tarantino et al (2006)	68 (NR)	14.9	34/68 (50)[e]	7/68 (10.3)	NR	NR	NR
Yiacoumettis (2005)	52 (52)	7	1/52 (1.9)	NR	NR	NR	NR

CI: confidence interval; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate.
a With or without replacement.
b Maxwell reported the total number; however, it is unclear whether this is a total of operations, implants or patients.
c 71/333 patients had implants replaced (21.3%).
d Hammond et al reported that 123 patients undergoing primary reconstruction had undergone prior breast surgery.
e 31/68 were associated with device.

Re-operation (FDA 2011a)

The cumulative incidence of implant removal with or without replacement reported in the Allergan study was 53.8 per cent (95% CI 43.6-5.3) at 10 years and 23.3 per cent (18.2-29.4) in the Mentor study at eight years (FDA 2011a). Table 25 details the cumulative incidence of both re-operation and

removal with or without replacement. Losses to follow up within the studies by Allergan and Mentor were substantial.

Table 25 Data from the FDA update, re-operation and implant removal (with or without replacement) (FDA 2011a)

	Allergan N=98 (losses to f/u 54) 10 years	Mentor N=252 (losses to f/u 100) 8 years
Re-operation	71.9 (61.5-81.4)	38.8 (32.9-45.5)
Implant removal with or without replacement	53.8 (43.6-65.3)	23.3 (18.2-29.4)

N: number of patients; f/u: follow up; all results are reported as Kaplan-Meier estimates with 95% confidence intervals.

Reasons for re-operation

Five studies reported reasons for re-operation (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Tarantino et al 2006; Yiacoumettis 2005). Tarantino et al (2006) reported that re-operation was related to capsular contracture (n=16), malposition or secondary dislocation (n=11), "routine" change of old prosthesis (n=2) and rupture or leakage (n=2). The average time to the first re-operation was 6.9 years and in 11 patients the prosthesis was exchanged twice (capsular contracture n=8, leakage n=1, technical failure n=1 and routine change n=1). Three patients with capsular contracture underwent three implant exchange procedures.

Cunningham and McCue (2009) did not report all reasons for re-operation; however, the most frequently reported primary reasons for re-operation were asymmetry (18.1%), capsular contracture (grades II/III/IV; 16.2%), biopsy (13.3%) and size change (10.5%; all as a percentage of the 105 re-operations).

Hammond et al (2012) provided a graphical representation of primary reasons for re-operation in reconstruction patients. Reasons included asymmetry, Baker grade III capsular contracture, breast mass or cyst, position dissatisfaction and wrinkling.

Maxwell et al (2012) reported reasons for any re-operation and implant removal (with or without replacement) which occurred in greater than 8 per cent of patients. For any re-operation the reasons included scarring (21.8%), capsular contracture (12.9%), implant malposition (12.1%), subject request for style/size change (9.7%), biopsy (5.8%), ptosis (4.8%) and haematoma/seroma (1.6%). For implant removal with or without replacement reasons included subject request for style/size change (32.1%), capsular contracture (16.1%), asymmetry (11.1%), implant malposition (8.8%), suspected rupture (6.2%), wrinkling/rippling (6.2%) and ptosis (2.5%).

Yiacoumettis (2005) reported only one implant replacement in the study period, which was performed with capsulotomy.

Overall capsular contracture, position dissatisfaction and patient request appear to be frequent reasons for re-operation amongst patients undergoing primary reconstruction with silicone-filled breast implants.

Other effectiveness

Three studies (Hammond et al 2012; Maxwell et al 2012; Spear et al 2007) reported other effectiveness outcomes and not all outcomes were reported by all studies. All three studies reported

results as Kaplan-Meier estimates only. Asymmetry and hypertrophic scarring were the only outcomes reported by more than one study. Results are summarised in Table 26 below.

Table 26 Effectiveness outcomes in primary reconstruction with silicone filled implants

	Hammond et al (2012)	Maxwell et al (2012)	Spear et al (2007)
Follow up (years)	6	6	6
Patients (implants)	191 (328)	225 (351)	98 (127)
Asymmetry	10.6 (6.7-16.7)	9.1 (5.9-13.8)	NR
Ptosis	5.8 (3.0-10.8)	NR	NR
Lack of projection	8.5 (5.1-14.1)	NR	NR
Excess skin tissue	4.3 (2.2-8.5)	NR	NR
Implant immobility	3.8 (1.7-8.2)	NR	NR
Loss of definition of inframammary fold	2.3 (0.9-6.1)	NR	NR
Shape distortion	1.6 (0.4-6.5)	NR	NR
Implant rotation	5.1 (2.5-10.0)	NR	NR
Hypertrophic scarring	2.5 (0.9-6.4)	NR	4.5 (1.7-11.5)
Upper pole fullness	NR	NR	NR

All information is presented as Kaplan-Meier estimates % with 95%confidence intervals; NR: not reported.

Other effectiveness (FDA 2011a)

The FDA update on the safety of silicone-filled implants reported effectiveness data at eight and 10 years post implantation of two core studies as well as a number of other effectiveness outcomes. These are summarised in Table 27 below.

Table 27 Data from the FDA update, other effectiveness outcomes in primary reconstruction (FDA 2011a)

	Allergan N=98 (losses to f/u 54) 10 years	Mentor N=251 (losses to f/u 100) 8 years
Asymmetry	23.2 (15.4-33.9)	NR
Dog ear scars from mastectomy	NR	1.6 (0.6-4.3)
Implant extrusion	NR	1.2 (0.4-3.7)
Implant malposition	2.3 (0.6-8.9)	2.6 (1.2-5.8)
Implant palpability/visibility	6.5 (0.4-17.0)	NR
Scarring/hypertrophic scarring	5.5 (2.3-12.7)	NR
Ptosis	0	NR

N: number of patients; f/u: follow up; all results are presented as Kaplan-Meier estimates with 95% confidence intervals.

Patient satisfaction

Patient satisfaction was reported by all studies involving primary reconstruction (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007; Tarantino et al 2006; Yiacoumettis 2005).

Tarantino et al (2006) used a non-validated questionnaire to determine patient satisfaction. The parameters included satisfaction regarding shape, size, consistency, acceptance, similarity to normal breast and scar on the breast. Other questions pertaining to donor site morbidity included shoulder function, shoulder force, discomfort and impairment of daily activities. Parameters with which the patients were most satisfied included shape, size, natural firmness and scar at donor site (Table 28, Table 29).

Table 28 Subjective responses to patient satisfaction questionnaire (51 patients), Tarantino et al (2006)

	Excellent (%)	Good (%)	Moderate (%)	Poor (%)	Very poor (%)
Shape	51	21.6	11.8	9.8	5.8
Size	51	25.5	11.8	7.8	3.9
Scar on the breast	52.9	21.6	17.7	3.9	3.9
Similarity to normal breast	29.3	11.8	11.8	21.6	25.5
Natural firmness	49	21.6	19.7	5.8	3.9
Acceptance	37.2	23.5	17.7	11.8	9.8
Evolution of shape	54.9	11.8	15.7	9.8	7.8
Scar at donor site	58.9	15.7	9.8	9.8	5.8

Table 29 Subjective responses to patients' judgement of donor-site morbidity, Tarantino et al (2006)

	Not at all (%)	Slight (%)	Moderate (%)	Severe (%)	Heavy (%)
Loss of shoulder force	49	15.7	9.8	17.7	7.8
Limitation in shoulder function	54.9	9.8	11.8	15.7	7.8
Impairment in daily activities	68.7	9.8	3.9	9.8	7.8
Discomfort	54.9	11.8	11.8	7.8	13.7

Hammond et al (2012) reported Kaplan-Meier estimates for the cumulative incidence of patient satisfaction at 10 weeks and annually through six years for primary (Table 30) and revision reconstruction (Table 35). For each parameter the level of dissatisfaction was always greater for the revision procedure as compared to the primary procedure.

Table 30 Cumulative incidence of patient satisfaction reported, Hammond et al (2012)

	Primary reconstruction KM % (95% CI)
Patient dissatisfied with aesthetic appearance of breast	5.1 (2.6-10.2)
Position dissatisfaction	2.1 (0.7-6.6)
Patient dissatisfied with feel of implant	1.7 (0.6-5.3)
Size change patient request	5.0 (2.6-9.4)
Patient would not have surgery again	NR

KM: Kaplan-Meier estimate; CI: confidence interval; NR: not reported.

Spear et al (2007) reported patient satisfaction as measured by a survey at six years for reconstruction patients (not delineated according to primary or revision). The study reported that 94 per cent of 102 patients surveyed were satisfied or extremely satisfied. Maxwell et al (2012) reported that 94.7 per cent of 184 patients surveyed were satisfied or extremely satisfied six years post-implantation.

The study by Yiacoumettis (2005) which reported on 52 patients who underwent two-stage reconstructions following bilateral mastectomies using silicone implants (manufacturer not reported) simply stated that "acceptance of and satisfaction with the results is considered high" and "The aesthetic appearance of the breasts is satisfactory" (Yiacoumettis 2005). Cunningham and McCue (2009) noted that through six years of follow-up 99.4 per cent of primary reconstruction patients indicated they would have the surgery again.

Revision reconstruction

Re-operation

The same studies also reported re-operation, explantation and replacement for patients who underwent revision reconstruction. Hammond et al (2012) reported only Kaplan-Meier estimates whilst some raw data were available in both remaining studies. Re-operation was a frequent outcome, reported or estimated to occur in greater than 10 per cent of patients (all studies) at long-term follow-up. Notably Maxwell et al (2012) reported a low estimate of explantation (1.9, 95% CI 0.3-12.6) suggesting that most patients probably had implants replaced whilst in Hammond et al (2012) an estimated 34.2 per cent had implants removed without replacement. Reasons for this were unclear. Results are summarised in Table 31.

Table 31 Re-operation in revision reconstruction with silicone filled implants

Author (year)	N(Ni)	Follow-up (years)	Total re-operation n/N (%)	Explanted[a] n/N (%)	Total re-operation KM % (95%CI)	Explantation only KM % (95%CI)	Replacement KM % (95%CI)
Hammond et al (2012)[b]	68 (113)	6	NR	NR	45.4 (34.0-58.5)	34.2 (24.0-47.3)[a]	NR
Maxwell (2012)	68 (112)	6	27	23	33.7 (23.6-46.6)	1.9 (0.3-12.6)	20.1 (12.2-32.1)
Cunningham & McCue (2009)	60 (NR)	6	21/60 (35%)	17/60 (28.3)	36.2 (25.2-50.1)	7.2 (2.7-18.0)	16.7 (9.0-29.8)

CI: confidence interval; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate.
a May be with or without replacement
b Hammond et al reported that 123 patients undergoing primary reconstruction had undergone prior breast surgery and that 63 patients in the revision reconstruction group had undergone prior breast surgery.

Re-operation (FDA 2011a)

The FDA update contained data regarding re-operation in patients undergoing revision reconstruction at eight and 10 years post implantation (FDA 2011a). The results are summarised in Table 32, below. The small patient numbers and substantial losses to follow-up are likely to have contributed to the lack of precision associated with estimates.

Table 32 Re-operation in revision reconstruction in the studies by Mentor and Allergan (FDA 2011a)

	Allergan N=15 (losses to f/u 7) 10 years	Mentor N=60 (losses to f/u 24) 8 years
Re-operation	20 (4.3-48.1)	29.0 (19.1-42.5)
Implant removal with or without replacement	46.7 (21.3-73.4)	40.8 (29.5-54.5)

N: number of patients; f/u: follow-up; all results are Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.

Reasons for re-operation

Three studies reported reasons for re-operation. Overall capsular contracture, implant malposition or asymmetry and patient requests for style or size change appeared to be the most frequently reported reasons for re-operation.

Maxwell et al (2012) reported a total of 27 re-operations. Twenty-three were for removal of the prosthesis (with or without replacement). Reasons for any re-operation (occurring in >8% of patients) were capsular contracture (22.2%), implant malposition (11.1%) and delayed wound healing (11.1%); subject request for style or size change (7.4%), scarring, haematoma/seroma and biopsy (all 3.7%). Reasons for implant removal (with or without replacement, occurring in > 8% of patients) were capsular contracture and subject request for size or style change (both 21.7%),

suspected rupture (13.0%), implant malposition (8.7%), wrinkling or rippling (8.7%) and asymmetry (4.4%).

Cunningham and McCue (2009) reported that among 34 re-operations (in 21 women) in the most frequently reported primary reasons for re-operation were biopsy (23.5%) and capsular contracture II/III/IV (14.7%). Hammond et al (2012) provided a graphical representation of primary reasons for re-operation in revision-reconstruction which included asymmetry, Baker grade III capsular contracture, position dissatisfaction, nipple complication, size change at patient request and wrinkling.

Other effectiveness

Only two studies (Hammond et al 2012; Maxwell et al 2012) reported other effectiveness outcomes (Table 34).

Table 33 Other effectiveness in revision reconstruction

	Hammond et al (2012)	Maxwell et al (2012)
Follow up (years)	6	6
Patients (implants)	68 (113)	68 (112)
Asymmetry	6.1 (2.3-15.6)	15.1 (8.1-27.2)
Lack of projection	13.7 (7.1-25.6)	NR

NR: not reported.
All results are presented as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.

Other effectiveness (FDA 2011a)

The FDA update on the safety of silicone-filled implants reported the results of two core studies which report effectiveness data at eight and ten years post implantation; both core studies report implant malposition (Table 34).

Table 34 Data from the FDA update, effectiveness outcomes in revision reconstruction (FDA 2011a)

	Allergan N=15 (losses to f/u 7) 10 years	Mentor N=60 (losses to f/u 24) 8 years
Asymmetry	6.7 (0.2-31.9)	NR
Dog ear scars from mastectomy	NR	3.4 (0.9-12.8)
Implant extrusion	NR	1.7 (0.2-11.3)
Implant malposition	13.3 (1.7-40.5)	6.7 (2.6-16.9)
Implant palpability/visibility	6.7 (0.2-31.9)	NR
Scarring/hypertrophic scarring	0	NR
Ptosis	0	NR

N: number of patients; f/u: follow up; all results are presented as Kaplan-Meier estimates % (95% confidence interval).

Patient satisfaction

All three studies reported patient satisfaction. Hammond et al (2012) estimated the cumulative incidence of patient satisfaction at 10 weeks and annually through six years using the Kaplan-Meier method for both primary and revision reconstruction (Table 35). Maxwell et al (2012) reported that 80.5 per cent of 55 patients surveyed were satisfied or extremely satisfied six years post-implantation and Cunningham and McCue (2009) noted that through six years of follow-up 94.4 per cent of revision reconstruction patients indicated they would have the surgery again.

Table 35 Cumulative incidence of patient satisfaction reported, as reported in Hammond et al (2012)

	Revision reconstruction KM % (95% CI)
Patient dissatisfied with aesthetic appearance of breast	8.4 (3.5-19.1)
Position dissatisfaction	4.6 (1.6-14.4)
Patient dissatisfied with feel of implant	3.8 (0.9-14.6)
Size change patient request	9.9 (4.5-20.8)
Patient would not have surgery again	NR

CI: confidence interval; NR: not reported; KM: Kaplan-Meier estimate

Permanent expanders

Primary reconstruction

Re-operation and reasons

Re-operation was reported in two studies (Chew et al 2010; Cicchetti et al 2006). Chew et al (2010) reported total re-operation associated with the device at five, 10 and 12.5 years with the rate of explantation steadily increasing over time until 100 per cent of expanders had been removed at 12.5 years (Table 36). Cicchetti et al (2006) reported a Kaplan-Meier six year estimate with no confidence intervals presented. Results for revision and primary patients were not separable. Goh et al (2012) reported that 69 patients underwent 105 re-operations, of which 62 were to exchange or improve cosmetic outcomes or to correct deformity. Capsule corrections due to pain or distortion were reported in 43 procedures.

Table 36 Re-operation with permanent expanders

Author (year)	N (Ni)	Follow-up (years)	Total re-operation n/N (%)	Explantation only n/N (%)	
Goh et al (2012)	240 (240)	5.4	69/240 (%)	NR	
Cicchetti et al (2006)[b,c]	97 (107)	5	NR	25[a] (NR)	
Chew et al (2010)	NR (68)	12.5	NR	76/76 (100)	
	NR (68)	10	NR	NR (94)	
	NR (68)	5	NR	NR (64)	
Total explantation according to radiotherapy status (Chew et al 2010)					
With radiotherapy	13 (NR)	5	NR	13/13 (100)	P <0.05 (X^2 test)
Without radiotherapy	55 (NR)	5	NR	33/55 (60)	

N: number of patients; Ni: number of implants; n: number of events: NR not reported.
a Kaplan-Meier estimate %, no CI reported.
b Cicchetti reported concurrent treatment with radiotherapy and chemotherapy both alone and in combination in 80% of reconstruction patients.
c Primary/revision NR

Other effectiveness

Cicchetti et al (2006) reported port valve complications, extrusion or exposure and contralateral procedures for patients undergoing primary reconstruction. Goh et al (2012) reported injection port complications in nine of 256 patients undergoing reconstruction (primary/revision not specified). Results are summarised in Table 37.

Table 37 Effectiveness in reconstruction with permanent expanders

	Cicchetti et al (2006)	Goh et al (2012)
Follow up (years)	5	5.4
Patients (implants)	NR (61)	240 (256)
Port valve complication n/N (%)	7/61 (11.5)	9/256 (3.5)[a]
Extrusion/exposure n/N (%)	3/61 9 (4.9)	NR
Contralateral procedures n/N (%)	21/61 (34.4)	NR

Outcomes are reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted, n: number of events; N: number of patients.
a Reported as number of implants.

Patient Satisfaction

Chew et al (2010) reported reasons for implant removal at five years post-operation in patients undergoing primary reconstruction and found that 23.5 per cent (16/68) of patients had their implant removed due to “poor aesthetics” and 8.8 per cent (6/68) because of “wrong size”.

Gui et al (2008) analysed patient satisfaction using a modified version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire BR-23 (QLQ BR-23) Body Image Subscale. Questions were asked about a range of parameters relating to body image, physical attributes, cancer worry and surgical choice. Only one outcome “dissatisfied with appearance of breast” was associated with a statistically significant change (15% at 1 year, 35% at 6 years; p=0.009) indicating that over time there was a deterioration in patient satisfaction relating to appearance of the breast. A total of 110 out of 123 patients completed the questionnaire (89.4% response). To determine whether there was a difference in satisfaction between patients who had different reconstruction techniques, Gui et al (2008) compared the quality-of-life scores between patients who had submuscular implant reconstruction (n=46, 41.8%) and those who had implant-assisted latissimus dorsi flap (n=64, 58.2%). There was no detectable difference in any of the parameters analysed using the QLQ BR-23 by surgery type apart from relative ease in finding a fitting bra in the latissimus dorsi compared with the submuscular implant group (p=0.03).

Revision reconstruction

One study reported results for patients undergoing revision reconstruction with permanent expanders (Cicchetti et al 2006) (Table 39).

Table 38 Revision reconstruction with permanent expanders

	Cicchetti et al (2006)
Follow up (years)	5
Patients (implants)	NR (46)
Port valve complication n/N (%)	1/46 (2.2)
Extrusion/exposure n/N (%)	0/46 (0)
Contralateral procedures n/N (%)	6/46 (13)
Wrinkling or rippling	2/46[a] (4.3)

n: number of events; N: number of patients.
a Calculated based on number of implants.

Subgroup analyses – prior or concurrent therapies

Five studies of patients undergoing implantation for reconstructive purposes (Benediktsson and Perbeck 2006; Chew et al 2010; Cicchetti et al 2006; Goh et al 2012; Tarantino et al 2006) reported at least one outcome according to prior or concurrent therapy status. These results are summarised in Table 39 below. Overall the included studies were characterised by poor reporting of prior and/or concurrent therapies. In patients who received expanders for either primary or revision reconstruction the incidence of capsular contracture was generally found to be higher in patients who received prior/concurrent treatment as compared to patients who received no treatment. Two studies reported the results of statistical tests for significance and in one study it is unclear whether such a test was performed.

Goh et al (2012) reported a statistically significant difference between rates of capsular contracture in the two groups ($p<0.0001$). The sample of patients undergoing prior/concurrent therapy was smaller than the sample who did not receive treatment. Benediktsson and Perbeck (2006) also found a significant ($p=0.012$) difference in the incidence of capsular contracture in patients receiving prior treatment as compared to no treatment. Tarantino et al (2006) did not report a test for significance between the two groups, and rates of capsular contracture appeared similar between the two.

Cicchetti et al (2006) was the only study comparing rates of wrinkling or rippling between patients who received prior or concurrent therapy to those who did not. Cicchetti et al (2006) reported a higher rate of wrinkling or rippling amongst patients who did not receive treatment than amongst patients who did; however, the sample size of patients who did not receive treatment was very small ($n=9$).

Chew et al (2010) reported the five year incidence of explantation in patients who had, or had not received radiotherapy and found the difference to be statistically significant ($p<0.05$). At five years post-surgery 100 per cent of patients who received radiotherapy had undergone explantation procedures as compared to 60 per cent of patients who had not received prior radiotherapy. This difference was not seen at 12.5 years follow-up at which point all patients had undergone an explantation procedure.

Table 39 Results of the prior or concurrent therapies sub-group analyses, reconstruction indication

Study	Implant type	Follow-up (years)	Outcome rate n/N (%)		p-value
			Prior/concurrent treatment[a]	No treatment	
Capsular contracture (III/IV)					
Cicchetti et al (2006)[b]	Expander	5	12/37 (32.4)	2/9 (22.2)	NR
Goh et al (2012)	Expander	5.4	13/25 (52)	38/177 (21.5)	p<0.0001
Benediktsson & Perbeck (2006)	Saline	5	10/24 (41.7)	12/83 (14.5)	p=0.012
Tarantino et al (2006)	Silicone	14.9	5/29 (17.2)	6/39[c] (15.4)	NR
Wrinkling/rippling					
Cicchetti et al (2006)	Expander	5	4/37 (10.8)[b]	2/9 (22.2)[b]	NR
Explantation					
Chew et al (2010)	Expander	5	13/13 (100)	33/55(60)	p<0.05

Results presented as the proportion of patients (n/N, %), unless otherwise specified: n: number of events; N: number of patients.
NR: not reported.
a Includes prior and/or concurrent treatment with radiotherapy and/or chemotherapy.
b Calculated based on number of implants.
c Assumed based on reported 16% of 68 patients of all patients who had III/IV (total n=11).

Augmentation indication

Description of included studies

A total of 20 studies that reported safety and/or effectiveness outcomes in patients undergoing breast implantation for augmentation purposes were included in this review. The studies have been grouped according to primary and/or revision indication, in addition to fill type of the device:

- primary augmentation with saline-filled implants;
- primary augmentation with silicone gel-filled implants;
- revision augmentation with silicone gel-filled implants;
- primary and revision augmentation with silicone gel-filled implants- *where the results were not reported separately for primary and revision augmentation*;
- mixed augmentation and reconstruction with silicone gel-filled implants- *where indications included both augmentation and reconstruction, with results not reported by indication*; and
- primary and revision augmentation with double-lumen implants.

Of the 20 studies, 17 were level IV case-series data; two were level III-2 evidence and one study was level II evidence (Table 40). In each of the level III-2 studies, only one arm of the study was included on the basis of the PICO criteria; in two of the studies (Pan et al 2012; Zoccali et al 2008), the control group included women who did not undergo breast implantation, with the comparator arm in the fourth study (Pfeiffer et al 2009) having insufficient follow-up. The level II evidence study, Niechajev et al (2007), randomised patients to one of two brands of implant, and as such, except for the manufacturer sub-group analyses, the evidence is considered level IV.

Five studies reported outcomes with the use of saline-filled implants, 15 with silicone implants and two using double-lumen implants (Several studies report outcomes for multiple implant types). The range of follow-up for the studies which used saline-filled implants was five to 23.7 years, with 2,104 patients included for primary augmentation purposes. Levi et al (2008) reported not the number of

patients enrolled, but rather the number of devices implanted (341). Follow-up ranged between five and 23.7 years for studies which reported outcomes for silicone-filled implants, with 22,098 patients included for the indication of primary augmentation, 585 patients for revision augmentation, 293 patients for primary and revision augmentation and 776 patients for mixed augmentation and reconstruction indications. The two studies (Pan et al 2012; Pfeiffer et al 2009) in which double-lumen implants were used had a range of follow-up of 7.3 to 23.7 years, with a total of 3,799 patients included.

FDA Allergan and Mentor studies (FDA 2011a)

The FDA update (FDA 2011a) on the safety of silicone gel-filled breast implantation additionally reported eight and 10 year follow-up of the Allergan and Mentor studies. The additional information provided in the FDA update has been included in the results. However it should be noted that this evidence has not been sourced from peer reviewed literature, the earlier studies (Spear et al 2007; Cunningham and McCue 2009) report six year data.

Table 40 Description of included studies, augmentation indication

Study Country	Level of evidence (P or R)	Manufacturer sponsored	Patient overlap	N (Ni)	Follow-up (years)	Losses to follow-up	Included for			
							Safety	Re-operation	Other effectiveness	Patient satisfaction
SALINE **Primary augmentation**										
Stevens et al (2005) United States	IV (R)	×	NR	324 (645)	5	None	✓	×	×	×
Levi et al (2007) United States	IV (R)	×	NR	NR (341)	6.04	NR	✓	×	×	×
Walker et al (2009) United States	IV (P)	✓	NR	901 (1800)	10	At five years: 25/901	✓	✓	✓	✓
SILICONE **Primary augmentation**										
Hammond et al (2012) United States	IV (P)	✓	NR	572 (1143)	6	At six years: 31%	✓	✓	✓	✓
Spear et al (2007) United States	IV (P)	✓	✓	455 (908)	6	Non-compliance at six years 19%	✓	✓	✓	✓
Murphy et al (2009) United States	IV (P)	✓	✓	455 (908)	6	Non-compliance at six years 19%	×	×	×	✓
Cunningham & McCue (2009) United States	IV (P)	✓	NR	552 (NR)	6	Non-compliance at six years 39%	✓	✓	×	✓
Maxwell et al (2012) United States	IV (P)	✓	NR	492 (983)	6	Non-compliance at six years 27%	✓	✓	✓	✓
Sevin et al (2006) Turkey	IV (R)	NR	NR	210 (420)	8	39 (19%)	✓	✓	×	✓
Dancey et al (2012) United Kingdom	IV (R)	×	NR	1369 (NR)	6	NR	✓	×	×	×
Araco et al (2007) United Kingdom	IV (R)	NR	NR	2270 (NR)	6.1	None	✓	✓	✓	✓

Study Country	Level of evidence (P or R)	Manufacturer sponsored	Patient overlap	N (Ni)	Follow-up (years)	Losses to follow-up	Included for			
							Safety	Re-operation	Other effectiveness	Patient satisfaction
Niechajev et al (2007) Sweden	II (P)	NR	×	67 (134)	5	NR	✓	×	×	×
Heden et al (2006a) United States	IV (R)	✓	NR	124 (NR)	6	None	✓	×	×	×
Zoccali et al (2008) Italy	III-2 (R)	NR	NR	15 (NR)	5.18	NR	✓	×	×	×
Revision augmentation										
Hammond et al (2012) United States	IV (P)	✓	NR	124 (247)	6	At six years: 34%	✓	✓	✓	✓
Spear et al (2007) United States	IV (P)	✓	NR	147 (288)	6	Non-compliance at six years 22%	✓	✓	✓	✓
Cunningham & McCue (2009) United States	IV (P)	✓	NR	145 (NR)	6	Non-compliance at six years 36%	✓	✓	×	✓
Maxwell et al (2012) United States	IV (P)	✓	NR	156 (310)	6	Non-compliance at six years 25%	✓	✓	✓	✓
Niechajev et al (2007) Sweden	II (P)	NR	×	13 (26)	5	NR	✓	×	×	×
Heden et al (2006a) United States	IV (R)	✓	NR	20 (NR)	6	None	✓	×	×	×
Primary and revision augmentation										
Heden et al (2006a) United States	IV (R)	✓	NR	144 (286)	6	None	✓	×	×	✓
Niechajev et al (2007) Sweden	II (P)	NR	×	80 (160)	5	Physical exam 20% Questionnaire 10%	✓	×	✓	✓
Collis et al (2007) United Kingdom	IV (R)	✓	NR	149 (298)	8.8	NR	✓	×	×	×

Study Country	Level of evidence (P or R)	Manufacturer sponsored	Patient overlap	N (Ni)	Follow-up (years)	Losses to follow-up	Included for			
							Safety	Re-operation	Other effectiveness	Patient satisfaction
Primary and revision augmentation and reconstruction										
de la Peña-Salcedo et al (2012) Brazil	IV (R)	NR	NR	507 (996)	6.8	None	✓	✓	✓	✓
Heden et al (2006b) Multiple European centres	IV (R)	✓	✓	106 (199)	8	None	✓	×	×	×
Heden et al (2009) Sweden	IV (R)	✓	✓	163 (300)	10.9	None	✓	×	✓	✓
DOUBLE LUMEN **Primary and revision augmentation**										
Pfeiffer et al (2009) Denmark	IV (R)	×	NR	203 (404)	7.3	None	✓	×	×	×
SALINE, SILICONE AND DOUBLE LUMEN **Primary augmentation**										
Pan et al (2012) Canada	III-2 (R)	NR	✓	24,558 (NR)	23.7	NR	✓	×	×	×

P: prospectively study design; R: retrospective study design; N: number of patients; Ni: number of implants; NR: not reported.
a NHMRC (NHMRC 2000)
✓ yes; ×: no

Critical appraisal

A summary of the standard checklist questions and results from the critical appraisal are presented in Table 41. Seven of the studies were prospective in design (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Murphy et al 2009; Niechajev et al 2007; Spear et al 2007; Walker et al 2009), with the same patient cohort shared by Murphy et al (2009) and Spear et al (2007). Four of these studies were large post-marketing surveillance studies sponsored by the manufacturers for the purpose of receiving FDA approval. Longer follow-up data presented to the FDA has additionally been reported. Twelve of the remaining studies were retrospective in design, and two were unclear as to their design.

Patient characteristics, in terms of indication for breast implantation, type of implants (manufacturer and fill-type) and surgical procedure, including positioning, were well reported. However, only four studies reported consecutive enrolment of patients. As the reporting of the manufacturer was typically performed, a sub-group analysis of rupture according to manufacturer may have been possible, had the results for the implants by different manufacturers been reported separately. In addition, whilst studies typically described implants as textured or smooth but outcomes were not reported accordingly, conclusions regarding the impact of surface type on safety and effectiveness outcomes could not be drawn. As textured implants may confer benefits with regard to a reduction in the incidence of capsular contracture, results for combined surface types may affect the interpretation of the results.

Adverse events were reported in 17 of the 20 studies included for breast augmentation. Outcomes ranged from rupture, capsular contracture, wrinkling and/or rippling to breast pain and breast-feeding outcomes (inadequate milk production). The post-marketing surveillance studies reported the most comprehensive catalogue of data with 12 studies reporting safety data only. Safety and effectiveness outcomes from the surveillance post-marketing studies generally did not report outcomes as incidence data; rather Kaplan-Meier estimates were presented which were calculated by conducting assessments in a sub-set of study participants. Fourteen studies reported implant rupture, the method of rupture detection varied; where reported, four of the 11 studies (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007) screened a subset of study participants by MRI to detect silent rupture, with rupture rates expected to be higher than in studies in which rupture was detected by clinical examination or patient report only. Methods of patient selection for MRI sub-studies were unclear. All patients in three studies (Heden et al 2006a; Heden et al 2009; Heden et al 2006b) were assessed for rupture by clinical examination and MRI. Reporting in one study was unclear as to whether MRI was used to confirm rupture alone, or whether all patients were routinely screened (Sevin et al 2006).

Capsular contracture was reported in 13 studies with consistent assessment and classification in 12 studies; one study, Dancey et al (2012), reported capsular contracture events as all who were classed as Baker scale grades II-IV, rather than Baker scale III-IV, which is more commonly considered for capsular contracture. Consequently, larger reported incidences of capsular contracture are anticipated from this study. Wrinkling and/or rippling was reported in eight studies.

Nine studies reported patient satisfaction and typically assessed satisfaction on a scale from definitely dissatisfied to definitely satisfied (or some variation). However, only one used validated

tools (Murphy et al 2009). Niechajev et al (2007) surveyed patients regarding their satisfaction with other parameters associated with implantation including size, appearance, scar location, changes in symmetry and sensation.

Table 41 Summary of critical appraisal, augmentation with all implant types

Critical appraisal				
Augmentation, all implant types (n=20)				
Question	**Yes**	**No**	**Unsure/Partial**	**Not applicable[a]**
Was the hypothesis/aim/objective of the study clearly stated?	20	0	1	0
Was the study conducted prospectively?	7	12	2	0
Were the cases collected in more than one centre?	10	8	3	0
Were participants recruited consecutively?	4	0	17	0
Were the characteristics of the participants included in the study described? (Reconstruction/augmentation; women)	21	0	0	0
Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	12	4	5	0
Did participants enter the study at a similar point in the disease?-	10	1	10	0
Was the implant of interest clearly described?	16	0	5	0
Was the surgical procedure clearly described?	15	4	2	0
Were additional interventions (co-interventions) clearly described (prior and concurrent treatments)?	3	18	0	0
Were all outcome measures established a priori?	18	3	0	0
Were the relevant outcomes assessed blinded to intervention status?-	3	6	12	0
Were the relevant outcomes measured with appropriate objective and/or subjective methods?	8	5	8	0
Method of rupture assessment (appropriate being surgical exploration or MRI)	7	3	1	10
Was a validated patient satisfaction tool used?	1	8	1	11
Was capsular contracture classified using the Baker scale and defined as grades III/IV?	11	1	0	9
Were the relevant outcomes (patient satisfaction) measured before and after the intervention?	1	18	0	2
Were raw data reported?	15	4	2	0
Was the nature of follow-up reported?	20	1	0	0
Was the loss to follow-up reported?	15	6	0	0
Did the study provide estimates of the random variability in the data analysis of relevant outcomes?	9	10	2	0
Were the adverse events related to the intervention reported?	12	6	3	0
Were both competing interests and sources of support for the study reported?	11	8	2	0

Modified critical appraisal checklist (IHE 2012).
n: number of studies.
a Or not assessed.

Safety

Capsular contracture

Overall, safety outcomes amongst the included studies were poorly and variable reported with the most consistent reporting associated with capsular contracture. In the context of this review

capsular contracture was defined as Baker's grade III or IV and where lower grades have been reported in the included studies those results are presented separately. Capsular contracture is a common complication following breast implantation, and correction of capsular contracture may require the surgical removal of the capsule by open capsulotomy and in some cases the removal and/or replacement of the implant.

Cancer incidence or recurrence of cancer

Although the development of cancer and recurrence of cancer have not been associated with breast implantation, concern has been raised about the potential of breast implants to mask the detection of breast cancer. A Canadian study (Lavigne et al 2011; Pan et al 2012; Xie et al 2010), which compared incident cancers and vital status of 24,558 women who received bilateral cosmetic breast implants, and 15,893 women who underwent other plastic surgery procedures, suggested that breast implants may delay the detection of breast cancer; however, the study did not find a statistically significant difference in survival between the breast implant and other plastic surgery groups. The recurrence of cancer or incidence of cancer within the included studies has been reported in the results of the safety analysis for completeness; however, it should be noted that this does not imply a causal relationship between the breast prosthesis or implantation procedure and the recurrence or development of cancer.

Primary augmentation with saline-filled implants

Two studies reported safety outcomes in patients who underwent primary breast augmentation using saline-filled implants (Pan et al 2012; Walker et al 2009). Walker et al (2009) enrolled 901 patients who were followed for up to 10 years after the procedure. Outcomes were assessed during the first five years at annual clinical examinations with surveys conducted annually thereafter (Table 42). Walker et al (2009) was the only study to report capsular contracture and wrinkling and/or rippling. The Kaplan-Meier risk estimate for capsular contracture increased from 11.4 per cent (95% CI 9.2-13.5) at five years, to 20.8 per cent (95%CI 18.1-23.8) at 10 years. The Kaplan-Meier estimate for wrinkling and/or rippling was only reported at five-year follow up and was 13.7 per cent (95% CI 11.3-16.1). Breast pain was reported during both follow-up periods. At five years the estimated Kaplan-Meier risk rate was 17.0 per cent (95% CI 14.5-19.5), which increased to 29.7 per cent (95% CI 26.6-33.0) by 10 years. Other safety outcomes reported in greater than seven per cent of patients within the initial five year follow-up included nipple sensitivity, skin hypersensitivity and loss of nipple sensation. No other safety outcomes were assessed by self-completion surveys at 10 years.

Pan et al (2012) reported 11 cases of breast cancer in saline implant subjects (n=879) during a follow-up of 20,489 person-years. No statistically significant difference in breast cancer rates for silicone versus saline implants (Incidence Rate Ratio (IRR): 0.74; 95% CI 0.4-1.37) was found.

Table 42 Safety in primary breast augmentation, saline-filled implants

	Walker et al (2009)[a]	
Follow-up (years)	5	10
Patients (implants)	901 (1800)	901 (1800)
Capsular contracture	11.4 (9.2-13.5)	20.8 (18.1-23.8)
Wrinkling and/or rippling	13.7 (11.3-16.1)	NR
Breast pain	17.0 (14.5-19.5)	29.7 (26.6-33.0)
Nipple hypersensitivity	9.8 (7.8-11.8)	NR
Skin hypersensitivity	7.6 (5.9-9.4)	NR
Loss of nipple sensation	9.9 (7.8-11.9)	NR

Note: reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.
NR: not reported.
a Outcomes occurring in <7% of patients were not reported.

Rupture

Three studies that assessed primary augmentation using saline-filled implants reported device rupture (Levi et al 2008; Stevens et al 2005; Walker et al 2009) (Table 43). Follow-up of the studies ranged between five to 10 years with patient numbers exceeding 100 at each timepoint. The study by Walker et al (2009) presented Kaplan-Meier estimates of deflation at both five and 10 years. Results of that study indicate that the risk of implant deflation increased over time.

Table 43 Rupture in primary augmentation with silicone gel-filled implants

Study	N (Ni)	Follow-up (years)	Rupture rate	
			n/N (%)	KM % (95% CI)
Stevens et al (2005)	324 (645)	5	48/645[a] (7.4)	NR
Levi et al (2007)	NR (341)	6.04	15/341[a] (4.4)	NR
Walker et al (2009)	901 (1800)	5	NR	6.8 (5.0-8.5)
Walker et al (2009)	901 (1800)	10	NR	13.8 (11.5-16.4)

CI: confidence interval; NR: not reported; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate
a calculated based on number of implants.

Rupture sub-group analyses according to manufacturer

Each of the three studies that assessed rupture used implants produced by a single manufacturer- Allergan in Walker et al (2009), and Mentor in the Stevens et al (2005) and Levi et al (2008) studies. The five-year Kaplan-Meier rupture rate of the Allergan implants was similar to the incidences of rupture in the studies that used the Mentor devices (Table 44).

Primary augmentation with silicone-filled implants

Safety outcomes in patients who underwent primary breast augmentation with silicone gel-filled implants were reported in seven studies (Araco et al 2007; Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Niechajev et al 2007; Sevin et al 2006; Spear et al 2007) (Table 44). An additional two studies reported breast cancer incidence(Heden et al 2006a; Pan et al 2012), with breastfeeding outcomes reported in one study (Zoccali et al 2008). Follow-up period of the studies reported in Table 44 ranged between five and eight years. All studies except one (Niechajev et al 2007) reported patient numbers greater than 100.

Capsular contracture was the most frequently reported safety outcome and was included by each of the seven studies. Kaplan-Meier risk estimates ranged between 2.4 per cent and 14.8 per cent (Table

44). Two studies reported occurrences of capsular contracture of 2.9% (Sevin et al 2006) and 9/2270 (0.40%) (Araco et al 2007). One study (Dancey et al 2012) reported capsular contracture using the definition of Baker's grades II/III/IV, and consequently observed a high incidence 333/1366 (24.4%; not shown in table as no other outcomes were reported). In contrast, the other seven studies reported capsular contracture using the definition of Baker's grade III and IV. Capsular contracture was a complication associated with reintervention. All eight studies that reported reasons for reintervention reported that capsular contracture was a common indication for re-operation. Four of the seven studies assessed wrinkling and/or rippling with three of these four studies reporting Kaplan-Meier estimates; whilst the study by Araco et al (2007) reported the incidence data (Table 44).

The second most frequently reported safety outcome was infection followed by haematoma and breast pain. Safety outcomes reported by Spear et al (2007) tended to be higher than other studies reporting similar outcomes. Other safety outcomes are reported in Table 45.

Breast cancer incidence was reported in two included studies (Heden et al 2006a; Pan et al 2012). Heden et al (2006a) reported that no subjects developed benign or malignant breast disease (n=124). Pan et al (2012) reported 284 cases of breast cancer in silicone implant subjects (n=16,111) per 356,975 person-years, and found no statistically significant difference in breast cancer rates for type of implant. A higher incidence rate ratio (incidence rate ratio 7.36; 95% CI 1.86-29.12) was identified using Poisson regression analysis for women receiving polyurethane coated silicone gel-filled implants when implanted in the sub-glandular position; however this ratio was calculated based on a limited number of incidences in a small patient cohort which is indicated in the large confidence interval.

Zoccali et al (2008) reported breast feeding outcomes and observed no significant differences for mean duration of breastfeeding in 15 silicone implant patients (26.1±4.12 weeks) compared with 15 control subjects without breast implants (26.0±4.71 weeks) (p=0.937). There was no significant difference in silicone concentration in the maternal milk of silicone implant patients (51.1±22.91 unit not reported) versus the control group without breast implants (51.1±18.60 unit not reported) (p=0.998), and there was no significant difference between the two groups for silicone concentration in whole blood (p=0.881) or for levels of inflammatory proteins (erythrocyte sedimentation rate: p=0.788; C-reactive protein: p=0.855; rheumatoid factor: p=0.588).

Primary augmentation with silicone-filled implants (FDA 2011a)

Longer follow-up results were presented by the FDA (FDA 2011a) (Table 45); follow-up was reported at 10 and eight years, respectively. The estimates of capsular contracture and breast pain were notably higher in the Allergan study as compared to the Mentor study (confidence intervals did not overlap). The reasons for this are not clear. Other safety outcomes are reported in Table 45.

Table 44 Safety in primary breast augmentation, silicone gel-filled implants

SILICONE							
Primary augmentation							
	Hammond et al (2012)[a]	**Spear et al (2007)[b]**	**Cunningham & McCue (2009)[c]**	**Maxwell et al (2012)[d]**	**Araco et al (2007)**	**Niechajev et al (2007)**	**Sevin et al (2006)**
Follow-up (years)	6	6	6	6	6.1	5	8
Patients (implants)	572 (1143)	455 (908)	552 (NR)	492 (983)	2270 (NR)	67 (134)	210 (NR)
Capsular contracture	2.4 (1.4-4.2)	14.8 (11.7-18.5)	9.8 (7.6-12.7)	4.6 (3.0-7.1)	9/2270 (0.40%)[e]	NR	6/210 (2.9%)[e]
Wrinkling and/or rippling	2.7 (1.6-4.5)[f]	1.2 (0.5-2.9)	NR	0.7 (0.2-2.0)	14/2270 (0.62)[e]	NR	NR
Infection	0.9 (0.4-2.1)	NR	1.6 (0.9-3.1)	1.7 (0.9-3.4)	20/2270 (0.9%)[e]	1/67 (1.5%)[e]	NR
Haematoma	1.2 (0.6-2.6)	NR	NR	1.1 (0.4-2.5)	25/2270 (1.1%)[e]	NR	NR
Breast pain	2.4 (1.4-4.1)[f]	9.6 (7.2-12.8)	NR	2.7 (1.5-4.7)	NR	NR	NR
Seroma	NR[h]	NR	NR	1.4 (0.6-3.0)	NR	2/134 (1.5%)[e,g]	NR
Swelling	NR[h]	8.3 (6.1-11.3)	NR	2.7 (1.5-4.7)	NR	NR	NR
Delayed wound healing	NR[h]	NR	NR	1.1 (0.4-2.6)	NR	NR	NR
Calcification	NR[h]	NR	NR	NR	NR	NR	4/210 (2%)[e]
Redness	NR	NR	NR	0.7 (0.2-2.0)	NR	NR	NR
Mass/cyst	5.9 (4.1-8.3)	NR	NR	NR	NR	NR	NR
Nipple sensation changes	4.4 (3.0-6.6)	NR	NR	NR	NR	NR	NR
Breast sensation changes	3.6 (2.3-5.6)	NR	NR	NR	NR	NR	NR
New diagnosis of rheumatic disease	7/572 (1.2%)[e,i] 1.4 (0.7-3.0)	NR	NR	NR	NR	NR	NR

Note: reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.
NR: not reported.
a Outcomes occurring in <1% of patients were not reported.
b Outcomes occurring in <5% of patients were not reported.
c Outcomes occurring in <10% of patients were not reported.
d Outcomes occurring in <2% of patients were not reported.
e Reported as a proportion of patients, n/N (%): n: number of events; N: number of patients.
f Mild occurrences were excluded.
g Calculated on number of implants.
h May have occurred in less than 1% of patients.
i Ten new diagnoses of rheumatic disease in 7 primary augmentation patients: spondyarthropathies (25 months), other connective tissue disease (35 months), Sjögren's syndrome (35 and 42 months), systemic lupus erythematosus (35, 42, and 44 months), fibromyalgia (36 and 37 months), and undifferentiated connective tissue disease (41 months).

Table 45 Data from the FDA update, summary results (FDA 2011a)

	Allergan	Mentor
Follow-up (years)	10	8
Number of patients	455	552
Losses to follow-up	269	291
Capsular contracture (Baker II)	NR	2.0 (1.1-3.7)
Capsular contracture (Baker III/IV)	19.1 (15.6-23.3)	10.9 (8.5-13.9)
Wrinkling and/or rippling	1.8 (0.8-3.7)	NR
Breast mass	NR	5.4 (3.7-7.8)
Breast pain	10.9 (8.2-14.3)	2.5 (1.5-4.3)
Breast/skin sensation changes	1.6 (0.8-3.3)	2.8 (1.7-4.5)
Bruising	0.4 (0.1-1.8)	NR
Delayed wound healing	1.1 (0.5-2.7)	0
Granuloma	NR	0
Haematoma	1.6 (0.7-3.2)	2.9 (1.8-4.8)
Infection	0.5 (0.1-2.1)	1.6 (0.9-3.1)
Inflammation of breast	NR	0
Irritation	0	NR
Lactation difficulties	NR	2.0 (1.1-3.8)
Metastatic disease	NR	0
Miscarriage	NR	2.9 (1.8-4.8)
Necrosis	0.2 (0-1.6)	NR
New diagnosis of breast cancer	NR	0
New diagnosis of rheumatic disease	NR	1.8 (1.0-3.5)
Nipple complications	6.3 (4.3-9.1)	0
Nipple sensation changes	NR	11.8 (9.3-14.8)
Pre-eclampsia at 36 weeks pregnant	NR	0
Redness	0.7 (0.2-2.0)	NR
Scarring/hypertrophic scarring	4.2 (2.6-6.5)	NR
Seroma/fluid accumulation	1.8 (0.9-3.5)	1.1 (0.5-2.5)
Skin rash	0.9 (0.3-2.3)	NR
Swelling	9.2 (6.8-15.0)	NR

Note: reported as Kaplan-Meier estimates % (95% confidence interval).
NR: not reported.

Rupture

Rupture was reported in seven primary augmentation studies that used silicone implants (Araco et al 2007; Cunningham and McCue 2009; Dancey et al 2012; Hammond et al 2012; Maxwell et al 2012; Sevin et al 2006; Spear et al 2007) (Table 46). The follow-up period of these studies ranged between six and eight years, with all studies reporting large patient numbers. Kaplan-Meier risk estimates for rupture at six years were based on the results from MRI sub-studies and had a range of 1.1 to 5.5 per cent. Hammond et al (2012) and Sevin et al (2006) reported incidences of rupture. Not all patients in the Hammond et al (2012) study underwent MRI screening to detect occurrences of silent rupture, and it is unclear whether Sevin et al (2006) used MRI to screen all patients for rupture or only to confirm suspected cases of rupture.

Table 46 Primary augmentation with silicone gel-filled implants

Study	N (Ni)	Follow-up (years)	Rupture rate	
			n/N (%)	KM % (95% CI)
Hammond et al (2012)	572 (1143)	6	5/572 (0.87)	2.1 (1.0-6.9)[a]
Spear et al (2007)	455 (908)	6	NR	5.5 (2.8-10.7)[a]
Cunningham & McCue (2009)	552 (NR)	6	NR	1.1 (0.3-4.3)[a]
Maxwell et al (2012)	492 (983)	6	NR	5.0 (2.4-10.2)[a]
Sevin et al (2006)	210 (NR)	8	8/210 (3.8)	NR
Dancey et al (2012)	1369 (NR)	6	NR	NR
Araco et al (2007)	2270 (NR)	6.1	NR	NR

CI: confidence interval; NR: not reported; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate
a Estimates based on MRI sub study.

Rupture (FDA 2011a)

Implant rupture was reported by the studies included in the FDA report (FDA 2011a) (Table 47). The estimate of rupture reported in the Mentor study has a large confidence interval (7.6 to 23.6%), reasons for this are unclear.

Table 47 Data from the FDA update, implant rupture (FDA 2011a)

	Allergan	Mentor
Follow-up (years)	10	8
Number of patients	455	552
Losses to follow-up	269	291
Implant rupture	10.1 (7.4-13.7)	13.6 (7.6-23.6)

Note: Kaplan-Meier estimates % (95% confidence interval).
NR: not reported

Rupture sub-group analyses according to manufacturer

Each of the seven studies reported the device manufacturer; five studies reported using devices made by a single manufacturer. Allergan manufactured those reported in the Spear et al (2007), Maxwell et al (2012) and Sevin et al (2006) studies, while Mentor manufactured those reported in Hammond et al (2012) and Cunningham and McCue (2009). Two studies reported using implants produced by two or more manufacturers, with Mentor and Eurosilicone producing those used in Araco et al (2007). Dancey et al (2012) reported using those manufactured by Allergan, Eurosilicone and Nagor (Table 48). No trends were identified in the results.

Revision augmentation with silicone gel-filled implants

Five studies reported safety outcomes in patients who underwent revision augmentation with silicone gel-filled implants (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Niechajev et al 2007; Spear et al 2007) (Table 48). One additional study reported breast cancer occurrence (Heden et al 2006a). They reported that no instances of benign or malignant breast disease were observed in patients who underwent revision augmentation with silicone gel-filled implants. The length of follow-up within these studies ranged between five and six years, with patient numbers exceeding 100, except for Niechajev et al (2007), who reported on 13 patients only.

The most frequently reported safety outcome was capsular contracture with Kaplan Meier estimates reported in four studies. Estimates ranged from 6.9 per cent to 22.4 per cent and studies reported that capsular contracture was a common reason for re-operation. Three of the five studies reported

Kaplan-Meier estimates for wrinkling and/or rippling which ranged from 2.7 to 5.9 per cent (Hammond et al 2012; Maxwell et al 2012; Spear et al 2007).

Infection was reported in four of the five studies and breast pain and swelling were reported in two. Risk estimates reported in Spear et al (2007) tended to be higher than other studies reporting the same outcomes. Other safety outcomes are reported in Table 48.

Table 48 Safety in revision breast augmentation with silicone-filled implants

	Hammond et al (2012)[a]	Spear et al (2007)[b]	Cunningham & McCue (2009)[c]	Maxwell et al (2012)[d]	Niechajev et al (2007)
Follow-up (years)	6	6	6	6	5
Patients (implants)	124 (247)	147 (288)	145 (NR)	156 (310)	13 (26)
Capsular contracture	9.7 (5.3-17.5)	20.5 (14.5-28.6)	22.4 (16.3-30.4)	6.9 (3.8-12.5)	NR
Wrinkling and/or rippling	5.9 (2.9-12.0)	3.9 (1.7-9.2)	NR	2.7 (1.0-7.1)	NR
Infection	2.1 (0.5-8.7)	NR	1.4 (0.4-5.6)	2.1 (0.7-6.3)	0/13 (0%)[e]
Haematoma	NR[f]	NR	NR	2.0 (0.6-6.0)	NR
Breast pain	NR[f]	9.6 (5.6-16.0)	NR	2.1 (0.7-7.2)	NR
Seroma	NR[f]	NR	NR	2.4 (0.8-7.5)	0/13 (0%)[e]
Swelling	NR[f]	7.3 (4.0-13.2)	NR	2.8 (1.0-6.3)	NR
Wound dehiscence	2.4 (0.8-7.4)	NR	NR	NR	NR
Delayed wound healing	1.2 (0.2-8.5)	NR	NR	1.3 (0.3-5.1)	NR
Calcification	1.1 (0.2-7.7)	NR	NR	NR	NR
Tenderness/soreness	1.3 (0.2-9.1)	NR	NR	NR	NR
Nipple complications	1.1 (0.2-7.4)	NR	NR	NR	NR
Redness	NR	NR	NR	0	NR
Mass/cyst	6.6 (3.2-13.5)	NR	NR	NR	NR
Nipple sensation changes	5.3 (2.4-11.4)	NR	NR	NR	NR
Breast sensation changes	2.7 (0.9-8.2)	NR	NR	NR	NR
New diagnosis of rheumatic disease	1.2 (0.2-8.4)[g]	NR	NR	NR	NR
Post-operative bleeding	NR	NR	NR	NR	1/13 (7.7%)[e]

Note: reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.
NR: not reported.
a Outcomes occurring in <1% of patients were not reported.
b Outcomes occurring in <5% of patients were not reported.
c Outcomes occurring in <10% of patients were not reported.
d Outcomes occurring in <2% of patients were not reported.
e Reported as proportion of patients, n/N (%); N: number of patients; n: number of events.
f May have occurred in less than 1% of patients.
g Fibrocystic disease.

Revision augmentation with silicone gel-filled implants (FDA 2011a)

The longer follow-up safety outcomes of revision augmentation in the Allergan Core Study and Mentor Core Study reported by the FDA are presented in Table 49. Nipple sensation changes was the highest reported safety outcome with a Kaplan-Meier estimate of 14.6 per cent (95% CI 9.7-21.8) in the Mentor study. Other outcomes reported include breast pain, 11.7 per cent (95% CI 7.1-18.9) reported by Allergan compared to 3.4 per cent (95% CI 1.3-8.8) reported by Mentor, and swelling, with 8.3 per cent (95% CI 4.6-14.5) reported in the Allergan study. Wrinkling was reported in the study by Allergan, with an estimate of 5.4 per cent (95%CI 2.6-11.0).Other safety outcomes are reported in Table 49.

Table 49 Data from the FDA update, safety in revision augmentation (FDA 2011a)

	Allergan	Mentor
Follow-up (years)	10	8
Number of patients	147	145
Losses to follow-up, n(%)	74 (50.3)	77 (53.1)
Capsular contracture (Baker II)	NR	6.2 (3.1-12.1)
Capsular contracture (Baker III/IV)	27.5 (20.3-36.6)	24.1 (17.7-32.3)
Wrinkling and/or rippling	5.4 (2.6-11.0)	NR
Breast mass	NR	6.5 (3.4-12.0)
Breast pain	11.7 (7.1-18.9)	3.4 (1.3-8.8)
Breast/skin sensation changes	2.2 (0.7-6.6)	1.4 (0.4-5.4)
Bruising	3.0 (1.1-7.8)	NR
Delayed wound healing	0.7 (0.1-4.8)	2.1 (0.7-6.3)
Granuloma	NR	2.4 (0.8-7.4)
Haematoma	2.1 (0.7-6.3)	2.8 (1.1-7.2)
Infection	1.4 (0.3-5.4)	1.4 (0.4-5.5)
Inflammation of breast	NR	1.4 (0.4-5.5)
Irritation	0.7 (0.1-5.0)	NR
Lactation difficulties	NR	1.6 (0.4-6.1)
Metastatic disease	NR	0
Miscarriage	NR	2.5 (0.8-7.6)
Necrosis	0	NR
New diagnosis of breast cancer	NR	1.8 (0.5-7.2)
New diagnosis of rheumatic disease	NR	1.7 (0.4-6.5)
Nipple complications	1.4 (0.3-5.4)	0
Nipple sensation changes	NR	14.6 (9.7-21.8)
Pre-eclampsia at 36 weeks pregnant	NR	1.1 (0.2-7.4)
Redness	0.8 (0.1-5.2)	NR
Scarring/hypertrophic scarring	6.6 (3.5-12.4)	NR
Seroma/fluid accumulation	6.0 (3.0-11.7)	2.1 (0.7-6.3)
Skin rash	0.7 (0.1-4.9)	NR
Swelling	8.3 (4.6-14.5)	NR

Note: reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.
NR: not reported.

Rupture

Rupture was reported in four included studies for revision augmentation with silicone gel-filled implants (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007) (Table 50). All Kaplan-Meier estimates of rupture were based on the results of MRI sub-studies and had a range of 2.3 to 11.6 per cent.

Table 50 Rupture in revision augmentation with silicone gel-filled implants

Study	N (Ni)	Follow-up (years)	Rupture rate	
			n/N (%)	KM % (95% CI)
Hammond et al (2012)	124 (247)	6	2/124 (1.6%)	2.9 (0.5-22.8)[a]
Spear et al (2007)	147 (288)	6	NR	2.3 (0.3-15.4)[a]
Cunningham & McCue (2009)	145 (NR)	6	NR	11.6 (5.4-24.2)[a]
Maxwell et al (2012)	156 (310)	6	NR	5.0 (1.3-18.4)[a]

CI: confidence interval; NR: not reported; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate.
a Estimates based on MRI sub study.

Rupture (FDA 2011a)

Extended outcomes in revision augmentation patients were reported by the FDA for the Spear et al (2007) (Allergan) and Cunningham and McCue (2009) (Mentor) studies. For the Mentor device the implant rupture rate at eight years was 15.5 per cent (95% CI 6.5-34.6) and the 10-year rate reported for the Allergan device was 6.3 per cent (95% CI 2.8-13.7).

Adverse event sub-group analyses according to manufacturer

Each of the three studies that assessed rupture were using implants produced by a single manufacturer- Allergan manufactured the implants reported in the studies conducted by Spear et al (2007) and Maxwell et al (2012), with Mentor reported as the manufacturer of the implants used in the Hammond et al (2012) and Cunningham and McCue (2009) studies (Table 51).

Table 51 Rupture and wrinkling and/rippling according to manufacturer

Study	N (Ni)	Follow-up (years)	Rupture rate		Wrinkling/rippling rate	
			n/N (%)	KM % (95% CI)	n/N (%)	KM % (95% CI)
Allergan						
Spear et al (2007)	147 (288)	6	NR	2.3 (0.3-15.4)[a]	NR	3.9 (1.7-9.2)
Maxwell et al (2012)	156 (310)	6	NR	5.0 (1.3-18.4)[a]	NR	2.7 (1.0-7.1)
Mentor						
Hammond et al (2012)	124 (247)	6	2/124 (1.6%)	2.9 (0.5-11.1)[a]	NR	5.9 (2.9-12.0)
Cunningham & McCue (2009)	145 (NR)	6	NR	11.6 (5.4-24.2)[a]	NR	NR

CI: confidence interval; NR: not reported; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate.
a Estimates based on MRI sub study.

Primary and revision augmentation with silicone-filled implants

Safety outcomes were reported in three studies, with the incidence of rupture, breast-feeding and reproductive adverse events reported (Collis et al 2007; Heden et al 2006b; Niechajev et al 2007). Of the 144 included primary augmentation and revision patients in Heden et al (2006a), 20 attempted to breast-feed, with 17.2 per cent having a problem. The most common breast-feeding problem both before and after implantation was inadequate milk production. One subject noted a problem in

both time periods. Reproductive problems after implantation were noted in six patients (4.2%) all of whom reported a reproductive problem before implantation.

Capsular contracture and wrinkling and/or rippling were not reported.

Three studies report the incidence of rupture in primary or revision augmentation with silicone gel-filled implants (Collis et al 2007; Heden et al 2006a; Niechajev et al 2007) (Table 52). Rupture was reported in each of the three studies and in one the method of rupture detection was not reported (Niechajev et al 2007).

Table 52 Rupture in primary or revision augmentation with silicone gel-filled implants

Study	N (Ni)	Follow-up (years)	Rupture rate	
			n/N (%)	KM % (95% CI)
Niechajev et al (2007)	80 (160)	5	0/80 (0)	NR
Heden et al (2006a)	144 (286)	6	1/144[a] (0.7)	NR
Collis et al (2007)	149 (298)	8.8	23/298[b,c] (7.7)	11.81 (7.2-16.5)[d]

CI: confidence interval; NR: not reported; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate
a Rupture occurred at 5 years after implantation, one additional indeterminate implant was additionally observed at five and at six years, respectively
b Calculated based on number of implants.
c Ruptured implants had a mean age 9.5 +/- 1.6 (range: 6.5-11.8), bilateral ruptures (n=4) occurred at 6.5, 8.0, 9.2 and 10.2 years, with the occurrence of unilateral ruptures (n=13) between 7.6-11.8 years.
d Cumulative probability of rupture at 13 years.

Rupture sub-group analyses according to manufacturer

The manufacturer was reported in all three studies. Two studies reported using implants produced by a single manufacturer, Allergan in Heden et al (2006a) and Mentor in Collis et al (2007). Niechajev et al (2007) reported using devices made from two manufacturers- Allergan and Eurosilicone (Table 53). Rates of rupture were highest in the study that used the Mentor devices. Similar methods of rupture detection (MRI, used in each patient) were reported in Collis et al (2007) (Mentor) and Heden et al (2006a) (Allergan).

Table 53 Rupture grouped by manufacturer

Study	N (Ni)	Follow-up (years)	Rupture rate	
			n/N (%)	KM % (95% CI)
Allergan				
Niechajev et al (2007)	40 (80)	5	0/32 (0)[a]	NR
Heden et al (2006a)	144 (286)	6	1/144[b] (0.7)	NR
Mentor				
Collis et al (2007)	149 (298)	8.8	23/298[c,d](7.7)	11.81 (7.2-16.5)
Eurosilicone				
Niechajev et al (2007)	40 (80)	5	0/32 (0)[a]	NR

CI: confidence interval; NR: not reported; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier
a Some patients (n=8) were lost to follow-up.
b Rupture occurred at 5 years after implantation.
c Calculated based on number of implants.
d Ruptured implants mean age 9.5 +/- 1.6 years (range: 6.5-11.8), bilateral ruptures (n=4) occurred at 6.5, 8.0, 9.2 and 10.2 years, unilateral ruptures (n=13) 7.6-11.8 years.

Mixed indication augmentation and reconstruction with silicone gel-filled implants

One study reported several safety outcomes (de la Pena-Salcedo et al 2012) for mixed breast implantation indications, and included patients who underwent primary and revision augmentation, in addition to those who underwent reconstruction with silicone-filled implants. The study enrolled 507 patients who received 996 implants with a polyurethane surface. Patients were followed for an average of 6.8 years, with all safety outcomes reported during this period as a proportion of the number of implants. Rash was the most frequently reported outcome, with an occurrence of 43/996 (4.3%) implants. A second study (Heden et al 2009) reported capsular contracture occurring in 5.3 per cent of patients in the study; all events were grade III capsular contracture. Outcomes are reported in Table 54 for these studies.

Two studies reported breast cancer incidence, reproduction and lactation issues (Heden et al 2009; Heden et al 2006b). Heden et al (2006b) stated that there were no findings of note regarding breast disease in the population (n=106) either before or after implantation. Heden et al (2009) reported that 16 per cent of the included subjects (n=163) had breast carcinoma prior to implantation, compared with 1.8 per cent after implantation.

Heden et al (2006b) stated that there were no findings of note regarding lactation or reproduction in the population either before or after implantation. Heden et al (2009) reported results that indicate implantation did not have a negative effect on lactation of reproduction. After implantation, 27 of the 163 included women reported attempted to breastfeed, and 22.2 per cent of those experienced a problem. Prior to implantation, 36.2 per cent of 94 women who attempted breast-feeding experienced lactation problems. The most common lactation problem was inadequate milk production.

Heden et al (2009) also reported reproductive outcomes, with 25.8 per cent of subjects experiencing reproductive problems before receiving their implants, and 8.6 per cent experiencing problems after implantation. Miscarriage was the most common reproductive problem both before and after implantation, and more than one-third of the women with a post-implantation reproductive problem (35.7 %) also had a pre-implantation problem.

Wrinkling was reported by two studies (de la Pena-Salcedo et al 2012; Heden et al 2009)although only a percentage is given in the study by Heden et al (2009).

Table 54 Safety in mixed indication augmentation and reconstruction with silicone-filled implants

	de la Peña-Salcedo et al (2012)	Heden et al (2009)
Follow-up (years)	6.8	8
Patients (implants)	507 (996)	163 (300)
Capsular contracture	4/996 (0.4)	NR (5.3) [a]
Wrinkling and/or rippling	18/996[b] (1.8)	NR (5) [b]
Infection	4/996 (0.4)	NR
Haematoma	6/996 (0.6)	NR
Seroma	8/996 (0.8)	NR
Wound dehiscence	0/996 (0)	NR
Rash	43/996 (4.3)	NR
Polyurethane related cancer	0/996 (0)	NR

Note: reported as n/N (%) unless otherwise denoted; n: number of events; N: number of implants.
a All Baker's III capsular contracture.
b Calculated based on number of implants.

Rupture

Three studies reported rupture with silicone implants (de la Pena-Salcedo et al 2012; Heden et al 2009; Heden et al 2006b) (Table 55**Error! Reference source not found.**). These studies included patients undergoing implantation for reconstructive or cosmetic purposes. The method of rupture detection was not reported in de la Peña-Salcedo et al (2012). Patients were assessed for rupture by physical examination and MRI in Heden et al (2006b) and Heden et al (2009).

Table 55 Rupture in augmentation or reconstruction patients

Study	N (Ni)	Follow-up (years)	Rupture rate	
			n/N (%)	KM % (95%CI)
Primary and revision augmentation and reconstruction (combined)				
de la Peña-Salcedo et al (2012)	507 (996)	6.8	7/996[a] (0.7)	NR
Heden et al (2009)	163 (300)	8	5/300[a,b](1.7)	NR
Heden et al (2006b)	106 (199)	10.9	12/199[a,d] (6.0)	NR

CI: confidence interval; NR: not reported; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate.
a Calculated based on number of implants.
b Ruptures occurred at 6 (n=1), 7 (n=1) and 8 (n=3) years post-implantation; two implants were unreadable by MRI.
d n=4 implants were indeterminate for rupture.

Adverse events sub-group analyses according to manufacturer

Each of the three studies reported using a single manufacturer, Allergan produced the devices reported in both Heden et al (2006b) and Heden et al (2009), while Silimed produced the implants reported in de la Peña-Salcedo et al (2012) (Table 56). No discernable trends were identified. Wrinkling and/or rippling were reported for the Silimed and Allergan devices and 18 of the 996 (1.8%) Silimed implants and five per cent of the Allergan implants developed wrinkling and/or rippling respectively.

Table 56 Rupture grouped by manufacturer

Study	N (Ni)	Follow-up (years)	Rupture rate	
			n/N (%)	KM % (95% CI)
Allergan				
Heden et al (2009)	163 (300)	8	5/300[a,b](1.7)	NR
Heden et al (2006b)	106 (199)	10.9	12/199[a] (6.0)	NR
Silimed				
de la Peña-Salcedo et al (2012)	507 (996)	6.8	7/996[a] (0.7)	NR

CI: confidence interval; NR: not reported; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate.
a Calculated based on number of implants.
b Estimates based on MRI sub study.

Primary and revision augmentation with double-lumen implants

One study, Pfeiffer et al (2009), reported safety outcomes in primary and revision augmentation patients who received double-lumen implants. The study enrolled 203 patients who were followed for an average of 7.3 years. Safety outcomes reported were capsular contracture, infection and seroma. The mean time to capsular contracture was 44.5 months (range 3-81.3 months) after implantation (Table 57). No other safety outcomes were reported.

Pan et al (2012) reported 68 cases of breast cancer in silicone implant subjects (n=3,596), during a follow-up of 100,944 person years, and found no statistically significant difference in breast cancer rates for type of implant.

Table 57 Safety in primary and revision augmentation with double-lumen implants

	Pfeiffer et al (2009)
Follow-up (years)	7.3
Patients (implants)	203 (404)
Capsular contracture	12/203 (5.9%)
Infection	14/203 (6.9%)
Seroma	6/203 (3.0%)

Note: all results are reported as n/N (%); n: number of events; N: number of patients

Effectiveness

Primary augmentation with saline-filled implants

One study by Walker et al (2009) assessed the effectiveness of saline-filled implants.

Re-operation and reasons

Re-operation outcomes reported by Walker et al (2009) included implant replacement and/or removal, in primary augmentation patients with saline-filled implants. The study reported a 25.9 per cent (95% CI 23.0-28.9) Kaplan-Meier risk estimate for total re-operation at five years. By 10 years, the estimate increased to 36.5 per cent (95%CI 33.4-39.9). Five-year risk estimates for implant replacement or removal were observed to be 11.8 per cent (95%CI 9.6-14.0), and at 10 years after implantation, this was estimated to increase to 20.2 per cent (95%CI 17.7-23.1). The most common reasons for augmentation re-operation (at 5 years) were deflation or capsular contracture. For those subjects who had their implants removed or replaced, the most common reasons were patient choice for style or size change (43.4% of 166 explants) or deflation (32.5% of 166 explants).

Other effectiveness outcomes

One study, Walker et al (2009), reported Kaplan-Meier estimates for other effectiveness outcomes at five years, including asymmetry (12.2%; 95% CI 10.0-14.4), implant palpability/visibility (12.1%; 95%CI 9.8-14.3) and implant malposition (9.2%; 95%CI 7.3-11.2).

Patient satisfaction

Patient satisfaction and quality of life was reported in one study (Walker et al 2009) that assessed the use of saline-filled implants in primary breast augmentation. The study reported that at ten years after implantation, 87.5 per cent of patients reported satisfaction with their implants, as defined by a response of either definitely satisfied, satisfied or somewhat satisfied. Furthermore, Walker et al (2009) reported the number of explantations due to patient request; dissatisfaction with style or size accounted for 43 per cent of 166 explants at five years, with similar results observed at 10 years (41.3 per cent of 300 explants).

Primary augmentation with silicone gel-filled implants

Seven studies reported effectiveness outcomes for primary breast augmentation with silicone gel-filled implants.

Re-operations

Re-operations were reported in six studies (Araco et al 2007; Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Sevin et al 2006; Spear et al 2007) (Table 58). Kaplan-Meier estimates were greater than 18 per cent across all estimates whilst Araco et al (2007) reported an extremely low incidence of re-operation of 1.6 per cent.

Table 58 Re-operation in primary augmentation with silicone filled implants

Study	Follow-up (years)	N (Ni)	Total re-operation (n/N, %)	Explanted[a] (n/N, %)	KM % (95% CI)		
					Total re-operation	Explantation	Replacer
Araco et al (2007)	6.1	3,002 (NR)	47/3002 (1.6)[b]	NR	NR	NR	NR
Hammond et al (2012)[c]	6	572 (1143)	NR	NR	18.1 (15.1-21.6)	7.0 (5.1-9.5)[a]	NR
Cunningham & McCue (2009)	6	552 (NR)	102/552 (18.5)[d]	37/552 (6.7)[e]	19.4 (16.3- 23.1)	4.0 (2.5-6.2)	3.9 (2.5-
Maxwell et al (2012)	6	492 (983)	109[f]	81[g]	19.4 (16.1-23.4)	0.7 (0.2-2.1)	9.6 (7.2-
Spear et al (2007)	6	455 (908)	NR	NR	28.0 (24.0-32.5)	2.8 (1.6-5.0)	10.0 (7.4
Sevin et al (2006)	8	210 (420)	21/210 (10.0)[g]	NR	NR	NR	NR

CI: confidence interval; NR: not reported; N: number of patients; n: number of events; Ni: number of implants; KM: Kaplan-Meier estimate
a With or without replacement in some studies.
b Includes data for 732 patients who had a PIP implant.
c Hammond et al reported that 12 primary augmentation patients had undergone previous breast surgery.
d 102 women underwent 135 re-operations.
e n: number of women; 37 women had a total of 66 explants.
f Maxwell reported the total number; however, it is unclear whether this is a total of operations, implants or patients.
g 16/210 had one revision only, 5/210 had two revisions.

Re-operation (FDA 2011a)

At eight years, the rate of total re-operation in the Mentor study was an estimated 20.1 per cent (95% CI 17.0-23.8) the 10 year results reported by Allergan were higher (36.1%;95% CI 31.6-40.9). The estimated rate of implant removal with or without replacement in the Allergan study (20.8%; 95% CI 17.2-25.2) was nearly triple that reported in the Mentor study (7.3%; 95% CI 5.3-9.9).

Table 59 Data from the FDA update, re-operation (FDA 2011a)

	Allergan	Mentor
Follow-up (years)	10	8
Number of patients	455	552
Losses to follow-up	269	291
Re-operation	36.1 (31.6-40.9)	20.1 (17.0-23.8)
Implant removal with or without replacement	20.8 (17.2-25.2)	7.3 (5.3-9.9)

Note: reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.
NR: not reported.

Other effectiveness and reasons for re-operation

Four studies (Araco et al 2007; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007) reported other effectiveness outcomes, including asymmetry, implant rotation, implant malposition, ptosis and scarring in patients undergoing primary augmentation with silicone-filled implants (Table 60). Asymmetry and hypertrophic scarring were the most frequently reported outcomes, reported in three studies Kaplan-Meier estimates for implant malposition were reported by two studies. Results are presented in Table 60.

Table 60 Effectiveness outcomes in primary augmentation with silicone filled implants

	Araco et al (2007)	Hammond et al (2012)[a]	Maxwell et al (2012)[b]	Spear et al (2007)[c]
Follow-up (years)	6.1	6	6	6
Patients (implants)	2270	572 (1143)	492 (983)	455 (908)
Asymmetry	6/2270 (0.3%)[d]	NR	0.8 (0.3-2.2)	3.0(1.8-5.1)
Ptosis	NR	14.6 (11.7 -18.0)	NR	NR
Scarring	NR	2.4 (1.4-4.1)	NR	NR
Implant rotation	NR	1.1 (0.5-2.4)	NR	NR
Hypertrophic scarring	NR	2.5 (1.5-4.3)	1.1 (0.5-2.7)	3.7 (2.3-6.0)
Implant malposition	NR	NR	2.3 (1.3-4.2)	5.2 (3.5-7.7)
Upper pole fullness	NR	NR	0	NR
Implant palpability	NR	NR	NR	1.6 (0.8-3.4)

Note: reported as Kaplan-Meier estimates % (95% confidence intervals) unless otherwise denoted.
NR: not reported.
a Outcomes occurring in <1% of patients were not reported.
b Outcomes occurring in <2% of patients were not reported.
c Outcomes occurring in <5% of patients were not reported.
d Reported as n/N (%):n: number of events; N: number of patients.

Other effectiveness (FDA 2011a)

The FDA presented other effectiveness outcomes observed in the Allergan and Mentor Core Studies. Both studies reported Kaplan-Meier estimates for implant malposition, with the 10-year rate observed in the Allergan study of 6.3 per cent (95% CI 3.9-8.4), compared to no instances reported by Mentor at eight years.

Table 61 Data from the FDA update, other effectiveness outcomes (FDA 2011a)

	Allergan	Mentor
Follow-up (years)	10	8
Number of patients	455	552
Losses to follow-up	269	291
Asymmetry	3.3 (2.0-5.1)	NR
Implant extrusion	NR	0
Implant malposition	6.3 (3.9-8.4)	0
Implant palpability/visibility	1.9 (1.0-3.8)	NR
Ptosis	2.0 (1.0-3.9)	NR

Note: reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.
NR: not reported.

Reasons for re-operation

Reasons for re-operation were reported by all studies reporting re-operation although the level of detail and nature of reporting varied. Hammond et al (2012) reported the five most common reasons for re-operation across any cohort (primary or revision augmentation or reconstruction) as breast mass/cyst, size change, asymmetry, position dissatisfaction and capsular contracture. Cunningham and McCue (2009) reported that among 135 re-operations (102 women) the most frequently reported primary reasons for any re-operation were capsular contracture grades II/III/IV (33.3%) and size change (14.8%), noting that all other reasons were reported in less than 10 per cent of cases. Sevin et al (2006) reported that six patients with Baker's grade III to IV required reintervention and that three patients with Baker's grade II required reintervention. Araco et al (2007) reported 47 re-operations of which the most common reasons were for capsular contracture, infection and breast asymmetry.

Both Maxwell et al (2012) and Spear et al (2007) reported the reasons for re-operation occurring in greater than eight per cent of any re-operation or implant removal (with or without replacement). Maxwell et al (2012) reported that the primary reasons for any re-operation were subject request for style/size change (17.4%), implant malposition (12.8%), scarring (11.9%), haematoma or seroma (10.1%), ptosis (9.2%), need for biopsy (7.3%), capsular contracture (6.4%) and delayed wound healing (2.8%). Spear et al (2007) reported the reasons for any re-operation as capsular contracture (27.5%), implant malposition (14.4%), ptosis (12.0%), biopsy (10.2%), haematoma or seroma (6.6%) and asymmetry (4.2%).

For implant removal (with or without replacement) Maxwell et al (2012) reported the reasons for removal as subject request for style or size change (49.4%), ptosis (12.4%), suspected rupture (11.1%), asymmetry (7.4%), capsular contracture (2.5%), implant malposition (2.5%) and wrinkling/rippling (1.2%). Spear et al (2007) reported the reasons for removal were capsular contracture (33.0%), patient request for style or size change (20.6%), implant malposition (10.3%), asymmetry (9.3%) and suspected rupture (9.3%).

Patient satisfaction

Patient satisfaction with silicone-filled primary augmentation was reported in seven studies (Araco et al 2007; Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Murphy et al 2009; Sevin et al 2006; Spear et al 2007) (Table 62). Sevin et al (2006) reported 190 of 210 patients (90.5%) to be extremely satisfied or satisfied with their implants, with 14/210 (6.7%) reported to be dissatisfied. Maxwell et al (2012) and Spear et al (2007) reported definite satisfaction and satisfaction in 95.1 per cent and 95 per cent of patients, respectively. When asked if patients would have the surgery again, 97.5 per cent of patients in the Cunningham and McCue (2009) study responded positively.

Hammond et al (2012) presented Kaplan-Meier estimates for a number of patient satisfaction parameters, including dissatisfaction with aesthetic appearance of the breast (2.8%; 95% CI 1.7-4.6), position dissatisfaction (2%; 95% CI 1.1-3.7) and dissatisfaction with the feel of the implant (1.1%; 95% CI 0.5-2.4). Hammond et al (2012) estimated that 3.7 per cent (95% CI 2.4-5.7) requested a size change.

Several studies used scales to grade patient satisfaction. Araco et al (2007) asked patients to grade their level of satisfaction using a Visual Analogue Scale of 0 to 10, with 0 indicating no satisfaction at all and 10 the maximum possible satisfaction. After an average of 6.1 years follow-up, patients reported mean (± standard deviation) satisfaction of 6.9 ± 1.6 (95% CI 6.9–7).

Murphy et al (2009) investigated a number of psychosocial outcomes in the primary augmentation cohort of the Spear et al (2007) study using the Body Esteem Scale (Franzoi and Herzog 1986) and the Rowland Scale (Rowland et al 1993) to evaluate body image, in addition to the Medical Outcomes Study 36-item Short Form Survey (SF-36) to measure health-related quality of life (Ware and Sherbourne 1992) (Table 63). The results of the Body Esteem Scale showed significant decreases in weight concern and physical condition and increases in sexual attractiveness at six years. Effect sizes were only small to moderate. Each of the three subscales within the Rowland Scale displayed significant improvements, with moderate effect sizes; however, significant deteriorations were observed in seven of the eight subscales of health-related quality of life, as assessed by the SF-36.

The only domain of the questionnaire to significantly improve was role limitation due to emotional problems. The authors noted that the small effect sizes would indicate that changes were unlikely to be significant (Murphy et al 2009).

Table 62 Patient satisfaction in primary augmentation with silicone filled implants

Study	N (Ni)	Follow-up (years)	Satisfaction n/N (%)	Measured
Sevin et al (2006)	210 (420)	8	190/210 (90.5%)[a]	Extremely satisfied or satisfied
Maxwell et al (2012)	492 (983)	6	NR (95.1%)	Definitely satisfied or satisfied
Spear et al (2007)	455 (908)	6	NR (95%)	Definitely satisfied or satisfied
Cunningham & McCue (2009)	552 (NR)	6	NR (97.5%)	Would have surgery again

NR: not reported; N: number of patients; Ni: number of implants; n: number of events.
a 14/210 (6.7%) reported to be dissatisfied.

Table 63 Psychosocial outcomes at six years (Murphy et al 2009)

Outcome measure	Scale range	Baseline Mean	6-year mean	p-value	Effect size
Body Esteem Scale					
Total score	32–160	121.5	119.8	p=0.063	N/A
Sexual attractiveness	13–65	49.5	51.1	p<0.001	0.37
Weight concern	10–50	34.8	33.5	p=0.006	-0.03
Physical condition	9–45	37.2	34.9	p<0.001	-0.12
Rowland Scale					
Improve self-image	1–5	3.0	3.4	p<0.001	0.47
Improve social relations	1–5	1.3	1.7	p<0.001	0.40
Improve daily living	1–5	2.6	2.9	p<0.001	0.36
Medical Outcomes Study 36-item Short Form Survey (SF-36)					
Outcome measure	**General population**	**Baseline Mean**	**6-year mean**	**p-value**	**Effect size**
Social functioning	81.5	96.7	92.5	p=0.001	-0.18
Vitality	58.4	74.8	68.2	p<0.001	-0.33
Mental health	73.3	83.9	81.6	p=0.004	-0.14
Physical functioning	81.5	98.3	95.2	p=0.001	-0.09
Role limitation due to emotional problems	79.5	64.6	89.7	p=0.002	-0.22
Role limitations due to physical problems	77.8	95.8	88.8	p<0.001	-0.06
General health	70.6	90.5	85.8	p<0.001	-0.25
Bodily pain	73.6	91.2	87.1	p=0.027[a]	N/A

N/A: not applicable, as significant changes were not observed
a Not regarded as statistically significant by the authors (the p level regarded as significant not stated by authors)

Revision augmentation with silicone-filled implants

Re-operation

Re-operation in revision augmentation patients who received silicone-filled implants was reported in four studies (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007) (Table 64). Cunningham and McCue (2009) reported 47 of 145 (32.4%) patients underwent 71 re-operation procedures. The four studies reported Kaplan-Meier estimates for total re-operation and Kaplan-Meier estimates were high in all instances. Replacement of the implant also appeared to occur frequently (Table 64).

Table 64 Re-operation in revision augmentation with silicone filled implants

Study	Follow-up (years)	N (Ni)	Total re-operation (n/N, %)	Explanted[a] (n/N, %)	KM % (95% CI)		
					Total re-operation	Explantation	Replacement
Maxwell et al (2012)	6	156 (310)	66[b]	56[b]	35.1 (27.9-43.6)	3.6 (1.5-8.5)	20.2 (14.4-28.0)
Cunningham & McCue (2009)	6	145 (NR)	47/145 (32.4%)[c]	24/145 (16.6%)[d,e]	34.2 (26.8- 43.0)	8.1 (4.6-14.3)	10.0 (5.9-16.9)
Spear et al (2007)	6	147 (288)	NR	NR	40.3 (32.5-49.1)	4.4 (1.9-10.4)	18.6 (12.8-26.5)
Hammond et al (2012)	6	124 (247)	NR	NR	24.1 (17.2-33.0)	13.6 (8.6-21.3)[d]	NR

CI: confidence interval; NR: not reported; N: number of patients; Ni: number of implants; n: number of events; KM: Kaplan-Meier estimate
a It could not be ascertained whether explantation was associated with replacement in some studies.
b Maxwell reported the total number; however, it is unclear whether this is a total of operations, implants or patients.
c 47 women underwent 71 re-operations.
d With or without replacement.
e 24 women had a total of 43 explants.

Re-operation (FDA 2011a)

Re-operation in the extended follow-up of the Allergan and Mentor studies was reported by the FDA (Table 65). At long term follow-up the rates of total re-operation and implant removal (with or without replacement) were substantial (greater than 20%).

Table 65 Data from the FDA update, re-operation (FDA 2011a)

	Allergan	Mentor
Follow-up (years)	10	8
Number of patients	147	145
Losses to follow-up	74	77
Re-operation	46.0 (38.0-54.9)	37.8 (30.2-46.6)
Implant removal with or without replacement	32.4 (25.0-41.3)	21.1 (15.0-29.2)

Note: reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.
NR: not reported.

Reasons for re-operation

Reasons for re-operation were reported re-operation although the level of detail and nature of reporting varied. Hammond et al (2012) reported the five most frequent reasons for re-operation across any cohort (primary or revision augmentation or reconstruction) as being breast mass or cyst, size change, asymmetry, position dissatisfaction and capsular contracture. Cunningham and McCue (2009) reported the most frequent reasons for re-operation amongst the 71 re-operations (in 47 women) as being capsular contracture (35.2%), size change (14.1%) and biopsy (12.7%).

Both Maxwell et al (2012) and Spear et al (2007) reported the reasons for re-operation that were responsible for more than eight per cent of any re-operation and of implant removal (with or without replacement). Maxwell et al (2012) reported the reasons for any re-operation (n=66)re-operation as being implant malposition (15.2%), capsular contracture (12.9%), scarring (10.6%), need for biopsy (10.6%), ptosis (9.1%), subject request for style/size change (7.6%), haematoma/ seroma (4.5%) and delayed wound healing (0%). The reasons reported by Spear et al (2007) were capsular contracture (18.1%), haematoma/seroma (13.8%), implant malposition (11.7%), ptosis (9.6%), biopsy (8.5%) and asymmetry (3.2%).

Reasons for explantation (with or without replacement) reported by Maxwell et al (2012) amongst 56 explantations were; subject request for style/size change (25%), capsular contracture (21.4%), suspected rupture (12.5%), implant malposition (107%), asymmetry (7.1%) and ptosis (3.6%). Spear et al (2007) reported reasons as being capsular contracture (22.6%), patient request for style/size change (18.9%), implant malposition (18.9%), suspected rupture (9.4%) and asymmetry (1.9%).

Other effectiveness

Other effectiveness outcomes for revision augmentation with silicone-filled implants were reported in three studies (Hammond et al 2012; Maxwell et al 2012; Spear et al 2007) (Table 66). In all studies Kaplan-Meier estimates for hypertrophic scarring and asymmetry were reported. Implant malposition and implant palpability were reported by two of the three included studies.

Table 66 Effectiveness in revision augmentation with silicone-filled implants

	Hammond et al (2012)[a]	Maxwell et al (2012)[b]	Spear et al (2007)[c]
Follow-up (years)	6	6	6
Patients (implants)	124 (247)	156 (310)	147 (288)
Asymmetry	1.7 (0.4-6.6)[d]	5.7 (2.9-11.2)	3.7 (1.6-8.7)
Ptosis	14.4 (8.7-23.4)	NR	NR
Scarring	2.2 (0.6-8.5)	NR	NR
Implant rotation	2.6 (0.9-8.0)	NR	NR
Hypertrophic scarring	3.5 (1.3-8.9)	2.7 (1.0-7.1)	6.1 (3.1-11.7)
Implant malposition	NR	6.1 (3.2-11.3)	6.2 (3.1-12.0)
Upper pole fullness	NR	1.4 (0.4-5.6)	NR
Implant palpability	3.5 (1.3-9.2)[d]	NR	7.5 (4.1–13.6)

Note: reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.
NR: not reported.
a Outcomes occurring in <1% of patients were not reported.
b Outcomes occurring in <2% of patients were not reported.
c Outcomes occurring in <5% of patients were not reported.
d Mild occurrences were excluded.

Other effectiveness (FDA 2011a)

Other effectiveness outcomes were reported by the FDA for extended follow-up of the Allergan and Mentor studies (Table 67); asymmetry had the highest Kaplan-Meier estimate, of 6.5 per cent (95% CI 3.2-12.8). Implant malposition was the only outcome reported by both Allergan and Mentor. Other effectiveness outcomes are reported in Table 45.

Table 67 Data from the FDA update, other effectiveness (FDA 2011a)

	Allergan	Mentor
Follow-up (years)	10	8
Number of patients	147	145
Losses to follow-up	74	77
Asymmetry	6.5 (3.2-12.8)	NR
Implant extrusion	NR	1.4 (0.4-5.5)
Implant malposition	6.0 (3.1-11.7)	2.5 (0.8-7.9)
Implant palpability/visibility	6.0 (3.0-11.6)	NR
Ptosis	4.9 (2.2-10.5)	NR

Note: reported as Kaplan-Meier estimates % (95% confidence interval), unless otherwise denoted.
NR: not reported.

Patient satisfaction

Patient satisfaction of revision augmentation with silicone-filled implants was reported in four studies (Cunningham and McCue 2009; Hammond et al 2012; Maxwell et al 2012; Spear et al 2007) (Table 68). Maxwell et al (2012) and Spear et al (2007) reported definite satisfaction and satisfaction in 88.8 per cent and 84 per cent of patients, respectively. When asked if patients would have the surgery again, 97.6 per cent of patients in the Cunningham and McCue (2009) study responded positively.

Hammond et al (2012) presented Kaplan-Meier estimates of patient satisfaction parameters, including dissatisfaction with aesthetic appearance of the breast (8.1%; 95% CI 4.1-15.7), position dissatisfaction (3.7%; 95% CI 1.4-9.7) and dissatisfaction with the feel of the implant (4.6%; 95% CI 1.9-10.7). The number of patients who requested a size change was an estimated 6.6 per cent (95% CI 3.4-12.8) with 1.2 per cent (95% CI 0.2-8.3) indicating they would not have the surgery again.

Table 68 Patient satisfaction in revision augmentation with silicone filled implants

Study	N (Ni)	Follow-up (years)	Satisfaction n/N (%)	Measured
Maxwell et al (2012)	156 (310)	6	NR (88.8)	Definitely satisfied or satisfied
Spear et al (2007)	147 (288)	6	NR (84)	Definitely satisfied or satisfied
Cunningham & McCue (2009)	145 (NR)	6	NR (97.6)	Would have surgery again

NR: not reported; N: number of patients; Ni: number of implants; n: number of events.

Primary and revision augmentation with silicone gel-filled implants

Re-operation

Re-operation was not reported in studies that reported outcomes for indications of primary and revision augmentation with silicone-filled implants.

Other effectiveness

Other effectiveness outcomes were reported in one study (Niechajev et al 2007) (Table 69). Of the 74 patients followed, three patients (4.1%) presented with scars that had widened to greater than four mm and required revision. A total of four of the 160 implants (2.5%) were associated with implant rotation and occurred in patients who underwent primary and revision augmentation (n=2 each).

Table 69 Effectiveness outcomes (Niechajev et al 2007)

	Niechajev et al (2007)
Follow-up (years)	5
Patients (implants)	80 (160)
Asymmetry	NR
Implant malposition	NR
Scarring	3/74 (4.1%)[a,b]
Implant rotation	4/160 (2.5%)[c,d]

Note: reported as proportions of patients, n/N (%), unless otherwise denoted; n: number of events; N: number of patients.
NR: not reported
a Some losses to follow-up reported.
b Scarring that required revision of the scar due to widening more than 4mm.
c Calculated on the number of implants.
d Two primary augmentation patients, two revision augmentation patients.

Patient satisfaction

Two studies reported patient satisfaction and quality of life measures for primary or revision augmentation indications with silicone-filled implants (Heden et al 2006a; Niechajev et al 2007) (Table 70). In the study conducted by Niechajev et al (2007), 73/74 (98.5%) patients reported they were very satisfied or satisfied with the procedure, while 97 per cent of the patients enrolled in the Heden et al (2006a) study indicated the surgery was very, quite or a bit advantageous. Patients also reported improvements (much, quite or a bit better) in other parameters. These included wearing clothes (99%) and body perception (95%). Ninety-six per cent of patients also reported feeling more feminine (much, quite or a bit more) following surgery. Parameters that were unchanged after breast implantation included physical health (74%), ability to remain active (72%) and working capacity (82%).

Table 70 Patient satisfaction in primary or revision augmentation with silicone-filled implants

Study	N (Ni)	Follow-up (years)	Satisfaction n/N (%)	Measured
Neichajev et al (2007)	80 (160)	5	73/74[a] (98.5)	Very satisfied or satisfied
Heden et al (2006a)	144 (286)	6	NR (97)[b]	Very advantageous, quite advantageous or a bit advantageous

NR: not reported; N: number of patients; Ni: number of implants; n: number of events.
a n=6 patients were lost to follow-up.
b NR (3%) reported that breast implant surgery was a bit disadvantageous or very disadvantageous.

Niechajev et al (2007) surveyed patients regarding their satisfaction with other parameters associated with implantation including size, appearance, scar location, changes in symmetry and sensation after five years. Patient's opinion on breast consistency, skin and nipple sensitivities were also sought (Table 71). Most patients were satisfied with their breast size (81%), and of the patients with preoperative asymmetry (n=35), 42 per cent observed an improvement after surgery. While 89 per cent of patients regarded the appearance of their scar as acceptable to very good, 42 per cent were not happy with its location, and predominantly considered it too high. With respect to breast consistency 26.4 per cent of the implanted breasts were viewed as either too soft or too firm. Patients judged breast skin and nipple sensitivity as normal in 71.6 per cent and 80.4 per cent of implanted breasts, respectively.

Table 71 Patient satisfaction (Niechajev et al 2007)

Characteristic	Responses				
Breast size[a]	Satisfied 52/64 (81%)	Too small 10/64 (16%)	Too big 2/64 (3%)		
Appear of scar	Very good 22/74 (30%)	Good 27/74 (36%)	Acceptable 17/74 (23%)	Bad 8/74 (11%)	
Scar location	Too high[b] 28/74 (38%)	Too low 3/74 (4%)	Satisfactory 43/74 (58%)		
Changes in asymmetry[c]	Improved 15/35 (42%)	No change 6/35 (18%)	Worse 7/35 (20%)		
Breast consistency	Soft 109/148 (74%)[d]	Firmer than desired 33/148 (22%)[d]	Too soft 6/148 (4%)[d]		
Breast skin sensitivity	Normal 106/148 (72%)[d]	Increase 4/148 (3%)[d]	Slight loss 36/148 (24%)[d]	Severe loss 2/148 (1%)[d]	No sensitivity 0/148 (0%)[d]
Nipple skin sensitivity	Normal 119/148 (80%)[d]	Increase 15/148 (10%)[d]	Slight loss 9/148 (6%)[d]	Severe loss 3/148 (2%)[d]	No sensitivity 2/148 (1%)[d]

Reported as a proportion of patients, n/N (%), unless otherwise denoted; n: number of events; N: number of patients.
a 64/80 patients were clinically examined at five years.
b too high or slightly too high.
c 35/80 patients had preoperative asymmetry, however only 28/35 were examined at five years.
d calculated based on number of implants.

Mixed indication augmentation and reconstruction with silicone-filled implants

Re-operation and reasons

Re-operation in mixed breast implantation indications with silicone-filled implants was reported in one study, de la Peña-Salcedo et al (2012). This study reported that 12 of 996 (1.2%) implants required additional procedures to treat implant rupture (n=7), capsular contracture (n=4) and implant malposition (n=1).

Other effectiveness

Other effectiveness outcomes, including asymmetry and implant malposition, were reported in two studies (de la Pena-Salcedo et al 2012; Heden et al 2009) (Table 72). Both studies reported on one outcome only.

Table 72 Effectiveness in primary and revision augmentation or reconstruction

	de la Peña-Salcedo et al (2012)[a]	Heden et al (2009)
Follow-up (years)	6.8	8
Patients (implants)	507 (996)	163 (300)
Asymmetry	NR	NR (7%)[b]
Implant malposition	8/996 (0.8%)[b]	NR

Note: reported as proportions of patients, n/N (%), unless otherwise denoted.
NR: not reported.
a All implants included had a polyurethane surface.
b Calculated on the number of implants.

Patient satisfaction

Three studies reported patient satisfaction in mixed indication breast implantation with silicone-filled implants (de la Pena-Salcedo et al 2012; Hammond et al 2012; Heden et al 2009) (Table 73). On a scale graded from one (most dissatisfied) to 10 (most satisfied), the final aesthetic result in the study conducted by de la Peña-Salcedo et al (2012) was 9.8, with patient satisfaction reported as 98

per cent. Hammond et al (2012) reported that 562/582 (96.6%) of patients would make the same decision to have the breast surgery. The surgery was reported to be advantageous in 91 per cent of patients enrolled in Heden et al (2009).

Other quality of life measures were reported in Heden et al (2009); where a seven-point scale was used to assess general and specific changes after implantation. Improvements were observed for the characteristics of body perception and wearing clothes (77 and 72%, respectively), while physical health, remaining active, working capacity and ability to exercise were predominantly unchanged. Ability to exercise and intimate experiences were reported to be worse in 10 per cent of patients.

Table 73 Patient satisfaction

Study	N (Ni)	Follow-up (years)	Satisfaction n/N (%)	Measured
Hammond et al (2012)	582 (NR)	6	562/582 (96.6%)	Would make the same decision to have this breast surgery
de la Peña-Salcedo et al (2012)	507 (996)	6.8	NR (98%)[a]	Scale graded from 1 (most dissatisfied) to 10 (most satisfied)
Heden et al (2009)	163 (300)	8	NR (91%)[b]	Reported surgery as advantageous

NR: not reported; N: number of patients; Ni: number of implants; n: number of events.
a Score of 9.8 on the 10 point scale.
b 4% reported disadvantageous and 5% neither.

Supplementary safety data

Anaplastic large-cell lymphoma (ALCL)

Two studies reported on the association between breast implants and anaplastic large-cell lymphoma (ALCL) (Largent et al 2012; Popplewell et al 2011). These studies have been summarised separately as they contain only information pertaining to the association between breast implants and lymphoma and no other implant-related data.

Popplewell et al (2011)

Popplewell et al (2011) retrospectively searched the files of the Departments of Pathology and Haematology/Hematopoietic Cell Transplantation database at the City of Hope for any pathologic or clinical diagnosis of primary T-cell lymphoma of the breast occurring in patients during the years 1999–2007. Of the 13 cases of primary T-cell breast lymphoma identified from the database, there were nine patients with ALCL, eight of whom had breast implants. The median patient age was 45.5 years (range 32 – 62). Implant types were usually not known; however, there were three confirmed saline implants and one confirmed silicone implant, and one was known to have a textured coating. Diagnosis of ALCL in the implant capsule occurred at a median of 7 years (range 5–30 years) following implant surgery.

Popplewell et al (2011) noted the risk of primary breast implant-associated ALCL could not be determined without epidemiological data but that eight of nine cases of primary breast ALCL had breast implants at a single institution. There was a high prevalence of ALCL anaplastic lymphoma kinase (ALK) negative histology in the occurrence of primary T-cell lymphomas in patients with breast implants, and the disease course was not always indolent in patients with tissue-associated disease, with several patients requiring multiple treatment regimens. Of the eight patients with breast implants at the City of Hope, two had complete remission whilst the outcome of the other six patients was unknown.

The authors reviewed the published literature and identified 24 documented cases of primary ALCL in patients with breast implants (14 patients implanted for cosmetic reasons, nine for reconstruction secondary to breast cancer (not lymphoma), and one unknown). Of these 24 cases, 11 implants were silicone, nine were saline, one was hydrogel, and three were of unknown composition. The search methodology for the review by Popplewell et al (2011) was not provided, and it is unclear if the search was systematic.

Largent et al (2012)

Largent et al (2012) examined the occurrence of ALCL and lymphoma in a large group of women with breast implants. The cohort of women enrolled in Allergan-sponsored multicentre breast implant clinical studies was analysed, and compared with lymphoma incidence in US women using the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program. Patient, procedure, and device characteristics were collected for six Allergan-sponsored breast implant clinical studies, which included 89,382 patients with follow-up, and 204,682 patient-years of follow-up. The studies predominantly used silicone-filled devices, with smooth or textured shells.

There were 28 cases of lymphoma among study participants, including 19 non-Hodgkin's lymphoma, four Hodgkin's lymphoma, and five lymphomas not otherwise specified. Using SEER database incidence data, the expected number of lymphomas in this population was 43, producing a standardised incidence ratio of 0.65 (28/43 (95% CI 0.43 – 0.94), P=0.02). This ratio suggests that there were significantly fewer cases of lymphoma observed among the implant population compared with the expected incidence based on US female population epidemiological data. When patients were stratified by cancer history at baseline, breast implant patients with or without prior cancer history did not experience a significantly greater incidence of lymphoma than the general US female population. Similarly, when patients were stratified by implant shell type, women with textured or smooth shell devices did not experience a significantly greater incidence of lymphoma than the general US female population.

Three of the 28 cases of lymphoma in the breast implant population were defined as ALCL, giving a crude ALCL incidence of 1.46 (95% CI 0.30–4.3) per 100,000 person-years. The three ALCL patients all had a history of breast cancer, had undergone primary or revision reconstructive breast implant surgery as part of an Allergan study (the Adjunct study), and were living two to three years after ALCL diagnosis. Using SEER estimates of ALCL rates in US female population from 1996 to 2007, the average annual incidence of primary breast ALCL was 4.28 (95% CI 3.51–5.05) per 100 million women aged 20 years or older, and 3.88 (95% CI 3.19–4.58) per 100 million females aged 15 years or older. During this period, 12 women who had no recorded history of cancer were diagnosed with primary breast ALCL; however, it is unknown whether they had received breast implants.

Largent et al (2012) noted study limitations, in particular a short follow-up period, but concluded that their results were in agreement with published prospective epidemiologic studies that suggested no evidence of an increased risk of lymphoma among women who received either textured or smooth shell breast implants.

Summary

A direct association between breast implants and ALCL remains inconclusive due to the rare occurrence of ALCL. The evidence base consists of low level studies, namely case series and case reports, and several large epidemiologic cohort studies. Systematic reviews on this topic are also restricted to these study types. The case series by Popplewell et al (2011) identified that the majority of ALCL cases at the single institution examined also had breast implants. Largent et al (2012) compiled data from several multi-centre breast implant studies, and found the incidence of lymphoma to be no higher in women with breast implants compared with that of the general US female population. The data were more limited regarding ALCL specifically, and Largent et al (2012) stated that the actual incidence of ALCL in US women with breast implants or with a prior breast cancer remains unknown. There is very little information available on the disease course and prognosis of ALCL in women with breast implants, or on the biological mechanism for the proposed link between breast implants and ALCL.

Summary of regulatory issues surrounding breast prostheses

Breast implants manufactured by Allergan and Mentor reflect the great majority of silicone-filled implants that have been available in the US. Other implants are relatively new to the market place, and have yet to publish any formal post-marketing approval data. A list of TGA approved implants is available in Appendix A. Silicone gel-filled breast implants that have been approved in the US by the FDA include Natrelle Silicone Gel-Filled Breast Implants (Allergan) and MemoryGel Silicone Gel-Filled Breast Implants (Mentor). The FDA required the manufacturers, Allergan and Mentor, to design and conduct six post-approval studies as conditions of marketing approval. The results of these studies have recently been made publically available in the FDA update (FDA 2011a). Post-approval studies required by the FDA included core studies, large studies, device failure studies, focus group studies, annual physician informed decision studies, and adjunct studies. Results of the core studies have been published for peer review; these studies have been included in this review, in addition to the extended follow-up results, as presented by the FDA. Thus the core studies will not be discussed in this section. Participants in large studies were enrolled in primary augmentation, primary reconstruction, revision augmentation, and revision reconstruction cohorts. The results of the large studies have not been included here as follow-up in these studies did not reach five years or more.

Large studies

The purpose of the large studies is to assess long-term outcomes and identify rare adverse events by enrolling more than 40,000 silicone gel-filled breast implant patients and following them for 10-years. These are ongoing and results are not yet available.

Device failure studies:

The purpose of the device failure studies was to evaluate silicone gel-filled breast implants that had been retrieved and returned to Allergan and Mentor. Allergan evaluated 2,665 devices of which 1,429 (53.6%) were found to be intact and functional, while 900 (33.8%) had openings in the shell, 158 (5.9%) had gel related defects, 91 (3.4%) had device surface defects and 87 (3.3%) could not be analysed. In the Mentor large post-approval study, 62 silicone gel-filled breast implants were retrieved, with 35 (56.5%) intact or without abnormality, and 27 (43.5%) with openings. In the Mentor core study, 97 devices were explanted and returned, with 73 (75%) intact and without abnormality, and 24 (25%) with damage or rupture.

Focus group studies:

The FDA required both Allergan and Mentor to complete focus group studies to improve the format and content of the labelling.

Annual physician informed decision studies:

The FDA required both Allergan and Mentor to institute a formal informed decision process to ensure that a woman obtained a patient information brochure with adequate time to read it prior to surgery, and that the surgeon had documented the patient was given an adequate understanding of the risks and follow-up recommendations associated with the device. Surveys in 2009 showed that physicians found the patients' brochures effective in communicating breast implant risks and benefits, but that not all physicians used the brochure.

Adjunct studies:

Women who received silicone gel-filled breast implants for reconstruction after mastectomy, correction of congenital deformities, or replacement of existing implants were enrolled in adjunct

studies from 1992 onwards (during the time period that these implants were removed from the market for other indications). The FDA summarised that data collection methodology and low follow-up rates (23% for Allergan and 16% for Mentor five years post-implant) limited data interpretation from these adjunct studies.

FDA conclusions from post-approval studies:

The main outcomes of interest to the FDA were adverse events associated with the procedure or device; key local complications and adverse outcomes from silicone gel-filled breast implants were capsular contracture, re-operation and implant removal. Other local complications included implant rupture, wrinkling, asymmetry, scarring, pain, and infection. Local complications observed in the post-approval studies were consistent with complications noted at the time of approval. Local complications or adverse outcomes became more likely the longer a woman had silicone gel-filled breast implants. Within 10 years of implantation, approximately one in five primary augmentation patients and one in two primary reconstruction patients required implant removal. In the post-approval studies, patient follow-up rates were lower than anticipated, which limited the ability to draw definitive conclusions and to detect rare complications. While very rare rates of complications could not be detected from the post-approval studies, there was no evidence to show that silicone gel-filled breast implants caused connective tissue disease or reproductive problems. Direct comparisons of the two approved silicone-filled breast implants were precluded, due to differences in study design, clinical endpoints, and patient populations.

Summary of findings from post-market surveillance of adverse events:

The primary aims of the FDA post-market medical device surveillance are to identify previously unrecognized adverse events and to help to detect patterns of actual or potential adverse events. The two silicone gel-filled breast implant manufacturers, Allergan and Mentor, are required to submit adverse event reports on silicone gel-filled breast implants through Medical Device Reports (MDR) or Postmarket Spreadsheet Reports (PSR). Patients and healthcare providers can also submit adverse event reports directly to the FDA.

The FDA received 133 individual MDRs associated with Allergan and Mentor silicone-filled breast implants between 2006 and 2010, which contained a total of 530 patient problem codes and 239 device problem codes. Events associated with these reports including two deaths, 84 serious injuries and 21 malfunctions. The FDA also received 16,681 reports associated with Allergan and Mentor silicone gel-filled breast implants through the PSR between 2006 and 2010, including 16,279 reports of injuries and 402 reports of implant malfunctions. A total of 26,511 patient problems were reported, with the patient adverse events most frequently reported including re-operation, capsular contracture, pain, infection and breast lumps. The primary reasons for re-operation were rupture, capsular contracture, implant malposition or asymmetry, infection, wrinkling and haematoma, and the primary reasons for implant removal were implant rupture, capsular contracture, malposition or asymmetry, infection, wrinkling and extrusion. A total of 12,327 device problem codes were reported in the PSR reports, with the most frequently reported device problems including device-patient incompatibility, rupture, implant malposition/asymmetry, and device defects that prevented the surgeon from implanting the device. The FDA summarised that the types of adverse events submitted were consistent with results from pre-market and post-approval studies. No unexpected

outcomes or complications were reported through December 2010, although there were rare reports of possible ALCL associated with breast implants.

Poly Implant Prosthèse (PIP) Implants/Australian context

Background

Poly Implant Prothèse (PIP) was a French company founded in 1991 that produced silicone breast implants in smooth and textured varieties. PIP implants were also marketed under the name M-implants and Rofil implants. They were found to contain an industrial silicone which violated formal manufacturing guidelines. Although they were considered third generation implants, they were considered to behave like second generation implants due to numerous early ruptures and heavy gel bleeds (Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) 2012). Implants were exported to Australia, Western European markets including Britain, Germany, Spain and Italy and Latin American countries such as Brazil, Venezuela and Argentina. The FDA never approved PIP implants (Coombes 2012).

Concerns surrounding the PIP implants first surfaced in France in 2009 when surgeons reported high rupture rates in this implant brand. A French health authority (Agence Francaise de Securite Sanitaire des Produits Sante (AFSSAPS)) and British Medicines and Health Care Regulatory Agency (MHRA) undertook an investigation into PIP and found the company had fraudulently used non-medical grade silicone (industrial silicone) in the implants (AFSSAPS 2011; MHRA 2010). This industrial silicone was different to the medical grade silicone component declared in the documents that were submitted by the company for conformity assessment. In March 2010, the French medical safety agency recalled PIP implants and the company was placed into liquidation due to the unapproved manufacturing process. Further insertion of PIP prostheses was then banned worldwide (SCENIHR 2012).

Australian Chief Medical Officer Report, April 2012

The TGA estimates that approximately 13,000 silicone breast implants manufactured by PIP have been supplied to the Australian market between 1999 and 2010. It is not known how many of these are currently implanted in women, nor how many women currently have this brand of implant, but an estimate of 5,000 women would appear reasonable. In parallel with the TGA's laboratory testing program, an expert panel was convened to provide specialist input into the review of evidence and further investigation of the safety of PIP implants; and a Clinical Advisory Committee provided advice on clinical measures, risks and benefits, and communication strategies in response to health concerns. A report conducted by the Australian Chief Medical Officer, Professor Chris Baggoley, presented the findings and results of testing of PIP implants conducted by the TGA (DoHA 2012).

In this report, no specific safety concern for PIP breast implants was identified from the particular toxicology, chemical tests or mechanical tests carried out (DoHA 2012). The gel and shell of tested PIP implants were found to be non-irritant; the tested PIP gels did not contain chemicals that were toxic to living cells; chemical testing showed in animal testing the amount of siloxanes (especially D4) in PIP implants were not a safety concern and metals in the PIP implants were not at a level of concern. Although mechanical tear elongation tests by French health authorities revealed PIP

implants were incompatible with the standard (SCENIHR 2012), the PIP implants similarly tested by the TGA were compliant with the designated international standard (DoHA 2012).

Variability in the physical and chemical characteristics of different batches of PIP implants was noted, and as of 8 November 2012 the TGA had received 435 confirmed cases of ruptured PIP implants (DoHA 2012; TGA 2012). The United Kingdom Department of Health concluded that PIP implants were significantly more likely to rupture or leak silicone than other implants by a factor of approximately two to six, with this difference being detectable within five years of implantation (Department of Health NHS Medical Directorate 2012). However, the Chief Medical Officer and a European report undertaken in light of PIP concerns found no such link (DoHA 2012; SCENIHR 2012).

A concern with the PIP breast implants was the use of industrial-grade silicone. This silicone included potentially toxic substances such as Baysilone, Silopren and Rhodorsil which are normally used as fuel additives or in the manufacturing of industrial rubber lining. French health authorities found PIP implants to have an irritant potential not found with the silicone gels from other prostheses (AFSSAPS 2011). Some consumers with PIP breast implants have reported experiencing systemic symptoms such as fatigue, hair loss and headaches; it is not clear whether there is a causal link to the industrial grade silicon.

The TGA did not find a specific serious safety concern with PIP breast implants. They also failed to find evidence for the existence of chemicals in PIP implants which are likely to cause harm to a woman or her unborn or breast-fed children. Unless women with PIP breast implants have medical complications associated with the implant (such as evidence that the breast implant has ruptured), the TGA suggest there is no medical reason to have them routinely removed. Despite claims that PIP implants are more likely to rupture, the TGA cannot confirm or exclude this possibility. There is also no evidence that the risk of ALCL in the breast for PIP implants is greater than for any other silicone gel filled breast implants. While there is no published evidence that silicone gel-filled implants cause connective tissue disease, the TGA is collecting further information on individual PIP reports.

Berry and Stanek (2012)

As a consequence of concerns relating to PIP prostheses, Berry and Stanek (2012) undertook a retrospective study of PIP product safety and durability in a population of women. Between January 2000 and July 2005, 453 consecutive patients in the UK underwent breast augmentation with PIP implants in a single centre in London. The device had been used for primary implantation in 209 patients, and for secondary procedures in 244 patients. A database of patients was constructed with attempts made to contact each patient to offer a free consultation and referral for ultrasound scan. Chief outcome measures included secondary surgery, the implant rupture rate and time to rupture. Contact was made with 273 patients (60.3%); 177 presented for a follow-up examination; 49 patients had prior explantation of their implants, 47 patients declined examination due to lack of concern and 180 patients were lost to follow-up.

Prior to the study, surgical intervention for rupture had occurred in 19 patients (4.2%), with a further 38 confirmed as a result of the study (8.4%). However, these findings were somewhat conservative as they assumed that the 180 women lost in follow-up did not have a rupture. The authors suggest that this figure is likely to be closer to seven per cent in the population contacted. An additional 15

patients (3.3%) were diagnosed with suspected rupture by ultrasound scan and were awaiting surgical confirmation, with 18 patients yet to undergo scanning.

The results of this study suggested that PIP implants have a rupture rate higher than equivalent devices and reawakened the debate for a more robust implant registry than a system of voluntary reporting.

Maijers and Niessen (2012)

Between 2000 and 2001, 475 patients underwent breast augmentation with PIP implants at the Jan van Goyen Clinic, Amsterdam. Medical records were used to trace manufacturer and implantation specifics. There were 112 women with 224 round, textured PIP implants (mean implant age 122 months) enrolled in this retrospective study, who underwent physical examination and MRI screening. Of enrolled patients, 363 were lost at follow up.

Physical examination suspected rupture in 12 women, with six confirmed by MRI. MRI screening in total identified 54 (24%) ruptured implants in 37 (33%) women, five of which presented with evidence of extra capsular leakage. The majority of the implant ruptures were asymptomatic (25/37, 67.6%). Of the 14 patients with capsular contracture Baker grade III, seven experienced rupture in at least one of their implants; additionally one patient with a Baker grade IV capsular contracture also had an implant rupture.

This study found the rupture prevalence rate for PIP implants after 10 years to be 24 per cent. Maijers and Niessen (2012) reported that this was higher than rates of most modern implants in the literature, but comparable to that of previous generations. The authors suggested that a shell of poor quality, rather than unauthorised silicone gel was the cause of the higher likelihood of rupture of PIP implants. They concluded that all PIP implants should be explanted due to this increased risk of rupture.

Araco et al (2007)

In the study conducted by Araco et al (2007), 3,002 patients received primary breast augmentation in Birmingham, United Kingdom between January 1996 and December 2001; of these, 732 were PIP implants. Araco et al (2007) undertook a retrospective study of this population in order to define complication rates and find associated factors in patients with a mean follow-up period for the entire cohort of 6.1 years, and mean age of 32.

Araco et al (2007) reported five main outcomes for the entire sample and presence of Haematomas, infections, breast asymmetry, rippling and capsular contracture. They also compared the PIP implants to those from other manufacturers complications observed for the entire cohort and for PIP implants alone, have been presented in Table 74. Occurrences of all complications reported were higher in patients who received PIP implants compared to the total cohort. Significant differences between PIP implants and those from other manufacturers were observed on univariate analysis for Haematoma, breast asymmetry and rippling ($p<0.05$). Of the total complications observed, patients with PIP implants accounted for 33 to 74 per cent, for rippling and breast asymmetry, respectively.

Table 74 Complications with PIP implants, as reported by Araco et al (2007)

Complication	Total occurrence	Occurrence with PIP implants	p-value
Haematoma	46/3002 (1.5%)	21/732 (2.9%)	p<0.05[a]
Infection	33/3002 (1.2%)	13/732 (1.8%)	NS
Breast asymmetry	23/3002 (0.8%)	17/732 (2.3%)	p<0.05[a]
Rippling	21/3002 (0.7%)	7/732 (1.0%)	p<0.05[a]
Capsular contracture (III/IV)	14/3002 (0.5%)	5/732 (0.7%)	NS

Reported as proportion of patients, n/N (%), unless otherwise reported, NS: not significant; PIP: Poly Implant Prothèse implants
[a] on univariate analysis only

Conclusions

Despite the safety fears of PIP breast implants, there is not enough evidence to conclude that women with PIP silicone breast implants have a greater risk to their health than women with other brands of implants. Despite much speculation, there is no conclusive evidence linking PIP implants to breast cancer, or other adverse health consequences. However, additional information is still needed to fully understand the associated rate of rupture and the effect a rupture may have on a woman's health. There is also concern about the highly variable nature of device manufacture for the PIP implant, which adds to the uncertainty for individual women. It should be emphasised that all silicone gel filled breast implants are considered high risk medical devices, and they all carry the risk of rupture over time. Although PIP implants were made with industrial-grade silicone, there is no solid evidence that this poses a safety concern to women with these implants. Australian tests to date have all been conducted in accordance with international standards with results showing PIP implants have met the safety standards required. In sum, PIP implants appear substandard due to the variability during manufacturing of the implants, although there is no evidence of a significant increased risk of clinical problems in the absence of rupture.

Economic analysis

No relevant literature was identified.

Summary of findings

Safety

Reconstruction

An assessment of the long-term safety of breast implantation for breast reconstruction was limited by the inconsistency of reported outcomes within the body of evidence. Safety outcomes reported in breast reconstruction patients were varied and trends in individual outcomes were difficult to identify.

Saline-filled implants

Two of the four studies assessing the safety of saline-filled implants for primary breast reconstruction presented results for capsular contracture. One study reported Kaplan-Meier estimates at five and 10-year follow-up and the other reported the incidence at five years. The data presented indicated that capsular contracture increases over time; and this was observed in the data at five-year follow-up compared with data at 10-year follow-up. In contrast, no studies evaluated revision breast reconstruction with saline-filled implants, so no comparisons could be drawn. The highest Kaplan-Meier estimate of wrinkling or rippling occurred in saline-filled implants as Walker et al (2009) reported a five-year Kaplan-Meier estimate of 24.6 per cent (95% CI 18.6-30.6)

Silicone gel-filled implants

Incidence and Kaplan-Meier estimate data indicated that capsular contracture and the likelihood of rupture both increase over a period of 10 years in the six studies available for analysis. In addition, wrinkling and rippling during follow-up was estimated to occur in approximately 10 per cent of cases. Three studies assessing revision breast reconstruction reported higher estimates of capsular contracture, wrinkling and rippling and rupture in patients undergoing revision breast reconstruction with silicone gel-filled implants in contrast to primary reconstruction patients; however, as no comparative data was available directly comparing these indications the accuracy and meaningfulness of this comparison cannot be quantitated.

The lowest reported estimate of wrinkling and rippling was observed in primary reconstructive patients receiving silicone gel implants (3.1%; 95% CI 1.4-6.9).

The Kaplan-Meier estimate for rupture reported for Allergan implants (in the FDA study) was higher compared to that calculated for Mentor implants, however, the follow-up duration for the study by Allergan was 10 years compared to the eight years recorded for Mentor implants.

Permanent expanders

Study participants across three studies receiving these breast prostheses for primary or secondary breast reconstruction had an increased incidence of capsular contracture at five years compared with the Kaplan-Meier estimates published for silicone gel and saline-filled breast implants at six-year follow-up.

Overall there was insufficient data available to observe a trend in any other outcomes in comparison to silicone gel and saline-filled breast implants. In addition, the available data pooled the results of

patients receiving permanent expanders for either primary or revision breast reconstruction, and as a result comparisons cannot be drawn.

Augmentation

Saline-filled implants

Two studies assessed the long-term safety of saline implants for primary breast augmentation. Calculated Kaplan-Meier estimates for capsular contracture increased over time and the estimates of breast pain increased from five to 10-year follow-up. Kaplan-Meier estimates of rupture ranged from four to 14 per cent at five to 10-year follow-up.

No studies reported safety of saline-filled breast implants for revision augmentation.

Silicone gel-filled implants

Seven studies reported safety outcomes of breast implantation with silicone gel-filled implants for primary augmentation, predominantly as Kaplan-Meier estimates. Capsular contracture was observed to increase over time and estimates of breast pain were lower for study participants receiving silicone gel-filled implants in comparison to saline-filled implants (highest estimate 10.9% versus 29.7% respectively). No trends were observed in the sub-group analysis by manufacturer.

In addition, reported Kaplan-Meier and incidence data for implant rupture was lower for silicone gel-filled compared to saline-filled breast implants for primary augmentation; however only three studies were available for evaluation and estimation of rupture for saline-filled breast implants in comparison to the seven studies available for silicone gel-filled implants.

In contrast to the results observed for primary versus secondary breast reconstruction, the adverse event rate for primary augmentation in comparison to revision augmentation was similar across the five studies included. Similar to the results of primary augmentation, an increase in capsular contracture over time was observed for revision augmentation with silicone gel-filled implants. Estimates of breast pain for revision augmentation were similar to those of primary augmentation, and were lower than the estimates for breast pain using saline-filled breast implants.

For the three studies reporting primary and revision augmentation as pooled results the most common adverse event was the incidence of breast feeding complications. Of the 20 women who attempted to breast-feed 17.2 per cent experienced difficulty. No estimates or incidences of any other adverse events were reported.

Two studies reported a number of safety outcomes relating to the use of silicone gel-filled implants for mixed augmentation and reconstruction patients and reported similar adverse event rates to the Kaplan-Meier estimates calculated for primary augmentation with silicone gel-filled implants.

Finally, only one study was available which reported the incidence of adverse events for double-lumen implants comprised of an inner lumen filling of silicone gel and an outer lumen filling of saline. The incidence of adverse events published in this study was unremarkable compared to the use of silicone gel-filled implants for either primary or revision augmentation.

No trends were identified between the results of different silicone gel-filled implants in the sub-group analysis according to manufacturer; as limited data was available for inclusion in these analyses. The highest rate of wrinkling or rippling occurred in saline-filled implants as Walker et al

(2009) reported a five-year Kaplan-Meier estimate of 24.6 per cent (95% CI 18.6-30.6), while the lowest rate was in primary reconstructive patients receiving silicone gel implants (3.1%; 95% CI 1.4-6.9). Estimates of wrinkling or rippling varied across all studies and no overall trends were identifiable.

Anaplastic large cell lymphoma

A direct association between breast implants and ALCL remains inconclusive, due to the rare occurrence of ALCL. The evidence base is composed of low level studies, namely case series and case reports, and several large epidemiologic cohort studies. Systematic reviews on this topic are also restricted to these study types. There is very little information available on the disease course and prognosis of ALCL in women with breast implants, or on the biological mechanism for the proposed link between breast implants and ALCL.

Effectiveness

Reconstruction

Saline-filled breast implants

The three studies reporting effectiveness outcomes of study participants receiving saline implants for primary reconstruction reported an increasing estimate of re-operation over time; with a maximum duration of follow-up of 12.4 years. Two studies reported the incidence of re-operation for any reason, and one reported this outcome as a Kaplan-Meier estimate with the highest estimate of 55 per cent at 10-year follow-up. The most common reasons for re-operation included capsular contracture and asymmetry reported across two of the three studies. The one study to estimate implant malposition and palpability and/or visibility reported a calculation of 17 per cent and 27 per cent respectively, at five year follow-up. In addition, the incidence of patient dissatisfaction was 25 per cent in the one study reporting this outcome at 10-year follow-up (Walker et al 2009).

No studies reported outcomes of revision breast reconstruction with saline-filled breast implants.

Silicone gel-filled implants

Seven studies reported effectiveness outcomes relating to primary reconstruction with silicone gel-filled implants. The re-operation rate ranged from 33 to 55 per cent, with incidence data available from four of the seven studies. Estimates and incidences of re-operation increased over time with the longest duration of follow-up 15 years. Similar reasons for re-operation were observed for silicone gel-filled implants in comparison to saline-filled implants; including capsular contracture, malposition and dissatisfaction with the style or size of implant. Whilst validated tools for measuring patient satisfaction were not used, and surveys varied greatly in content and structure, study participants generally self-reported satisfaction as a result of implantation.

Estimates of re-operation following revision breast reconstruction with silicone gel-filled implants were similar to those reported for primary breast reconstruction. As with primary reconstruction re-operation increased over time with the longest duration of follow-up 10 years; with similar reasons for re-operation.

Permanent expanders

Two studies examined the use of permanent expanders for patients undergoing either primary or revision breast reconstruction; and effectiveness results were pooled for both indications. At 12.5-year follow-up all permanent expanders implanted had been removed in study participants across both studies. Twenty-five per cent of expanders were removed due to poor aesthetics. Other reasons include deterioration of patient satisfaction over time following implantation.

Prior therapy before primary breast reconstruction

Three studies reported prior radiation therapy and one study reported prior and/or concurrent radiation therapy in conjunction to primary breast reconstruction. Two of the four studies reported prior radiation therapy before either primary or revision breast reconstruction, of which one used permanent expanders and the other silicone gel-filled implants. One study by Cichetti et al 2006 included patients undergoing prior radiotherapy therapy alone or in association with chemotherapy which accounted in 27 per cent of patients. The results for these studies reporting a mixed patient population were similar to those reporting primary reconstruction only.

Overall patients undergoing prior or concurrent radiation therapy in conjunction with breast reconstruction reported poorer outcomes due to higher incidences of implant wrinkling and rippling, re-operation and explantation.

Augmentation

Due to the number of different indications it was difficult to draw conclusions regarding effectiveness outcomes for saline-filled compared to silicone-filled breast implants. The lack of comparative data further limited the ability to identify trends in the data.

Saline-filled implants

Only one study reported the effectiveness of saline-filled breast implants (Walker et al 2009). The Kaplan-Meier estimate for re-operation for any reason was 26 per cent at five years and by 10 years had increased to 37 per cent. Five-year Kaplan-Meier estimates also increased for implant replacement and removal and by 10 years were estimated at 20.2 per cent. The most common reason for re-operation was deflation or capsular contracture. For study participants who elected to remove and/or replace implants the reasons were style or size change.

No data was reported for revision augmentation using saline-filled implants.

Silicone gel-filled implants

Six studies reported the effectiveness of silicone gel-filled implants for primary augmentation. The incidence of re-operation ranged from 1.6 to 18.5 per cent in contrast to the Kaplan-Meier estimates which ranged from 18.1 to 28 per cent, all at six-year follow-up. Kaplan-Meier estimates for re-operation increased to 36.1 per cent at 10-year follow-up for Allergan silicone gel-filled implants. Common reasons for re-operation were similar to those reported for saline-filled implants and included capsular contracture, breast mass or cyst, size or style change, asymmetry or position dissatisfaction.

Similar to results for the use of silicone gel-filled implants for breast reconstruction, patient satisfaction for primary augmentation with silicone gel-filled implants was not assessed using validated tools and surveys varied greatly in content and structure; however study participants generally self-reported satisfaction as a result of implantation across the four studies included.

Four studies assessed revision augmentation with silicone gel-filled breast implants. The one reported incidence of re-operation at six years was higher compared to the incidence and Kaplan-Meier estimates reported at six-year follow-up for primary augmentation patients (32.4% versus 18.1-28.0% respectively). Kaplan-Meier estimates for re-operation for these patients were also higher at six-year follow-up; however reasons for re-operation were similar to those undergoing primary augmentation. In contrast, estimated explantation rate for revision augmentation patients was similar to those undergoing primary procedures.

Re-operation was not reported for study participants receiving silicone gel-filled implants for mixed primary and revision augmentation in the three studies which assessed this patient population. Evaluation of other effectiveness outcomes by these authors was similar to the results reported for primary augmentation patients only.

Two studies reported effectiveness outcomes as incidence data for the mixed indication of breast augmentation and reconstruction; of which one reported re-operation. Twelve of 996 implants required re-operation due to implant rupture (n=7), capsular contracture (n=4) and implant malposition (n=1). All other effectiveness outcomes were similar to results published for primary augmentation with silicone gel-filled implants.

Discussion

Limitations of the evidence

The aim of this rapid review was to assess the long-term safety and effectiveness of breast prosthesis implantation for reconstructive and cosmetic purposes, with a focus on evaluation of the in vivo lifespan of breast implants. A total of 28 studies were included in this rapid review: 12 studies reported on augmentation patients only; nine reported on reconstructive patients only; four reported on augmentation and reconstructive patients separately and three reported on patients receiving prostheses for either indication. The conclusions which can be drawn from the data presented in this rapid review is limited by the paucity of long-term studies reporting incidence data for the safety and effectiveness of breast implants across all indications and implant types. Furthermore the evidence base was predominantly comprised of poorly designed retrospective case series data obtained via case note review. Additional origins of heterogeneity within the data included poor reporting of prior or concurrent therapies in patients undergoing breast reconstruction, implant characteristics, methods of assessing outcomes and the lack of baseline assessment for patient satisfaction.

Trends observed in the available data are based on calculated Kaplan-Meier estimates reported by study authors. These estimates are calculated by conducting assessments of patient outcomes in a subset of study participants, and include 95 per cent confidence intervals. Methods for selecting study participants for inclusion in sub-studies were not reported by any authors, and as a result the validity and applicability of the results of these sub-studies to the total study population within these included studies is not possible.

The Kaplan-Meier estimates reported by authors throughout the included studies indicate a low level of precision given the large confidence intervals; and this may be a result of a small number of study participants included in the sub-studies resulting in imprecise estimates across the total study population.

The lack of comparative study data limited the conclusions which can be ascertained across the implant types as well as surgical approach, implant placement and the impact of prior therapy for patients undergoing breast reconstruction.

Outcomes were predominantly reported at six-year follow-up, with limited data available beyond this time-point. In addition, more data was available regarding the use of silicone gel and therefore conclusions which can be drawn regarding saline-filled and expander implants are limited by the quantity of evidence published. Also, further prospective studies assessing the outcomes of revision augmentation and reconstruction would be beneficial, as less data was available for these indications.

Methods for assessing rupture were insufficiently described within the majority of the included studies for all indications. As rupture can occur silently, namely first as intracapsular contracture which can ultimately result in extracapsular leakage of the implant contents, MRI is the gold standard for assessing whether an implant has ruptured. As a number of the included studies conducted patient self-assessment or clinical examination only within the subset studies designed to calculate the Kaplan-Meier estimates for the total study population; it is unclear whether these

estimates represent the true incidence of rupture long-term. In addition, as limited detail was provided in a number of studies, and due to the retrospective design of a number of the case series studies, it is difficult to determine whether rupture occurred due to surgical causes, such as at the time of explantation or due to mechanical trauma.

Whilst the surgical technique and placement of the breast prostheses was reported in 25 of the 28 included studies, many authors placed implants in different sites using the same implant type and so no trends could observed in the data. As a result, the impact of surgical technique and placement chosen for implantation of breast prostheses is an area for further research.

Patient satisfaction assessment within the included studies was relatively subjective, as only one study used validated tools and data was predominantly based on patient self-assessment using surveys; and the content and structure of these surveys was variable or not reported. In addition, structured assessment tools tailored to breast implantation, such as the Breast Q assessment tool, were not used by study authors. In addition, baseline measures and any comparison to baseline post-implantation were not reported, thus the validity of the majority of results to assess satisfaction may be compromised. The one study (Murphy et al 2009) which used three validated assessment tools, namely the Body Esteem scale, the Rowland scale and the Short-Form 36 (SF-36); also drew comparisons to baseline (primary augmentation indication). In future, studies currently underway using tools such as the Breast Q measurement tool may contribute to the evidence base data regarding the long-term satisfaction of breast implantation according to indication, where currently there is a paucity of quality data.

A confounding factor affecting the results of breast implantation across all prostheses types was the poor reporting of prior or adjuvant radiation or chemotherapy in women undergoing primary or revision breast reconstruction. Of the 14 studies which included patients undergoing breast reconstruction only five reported whether patients had received prior or concurrent therapy and the type of therapy. In addition, only four of these five studies reported the outcomes of capsular contracture, and wrinkling or rippling according to treatment status. Reporting of the nature, timing and duration of prior or concurrent breast cancer treatment by future studies would contribute positively to the evidence-base.

Overall, the methods used to identify rupture in the included studies appeared to be insufficient as only some studies assessed silicone gel-filled implants utilising MRI. In the other included studies for saline-filled and permanent expander implants methods used to assess rupture varied from clinical follow-up to telephone interviews or reports to the manufacturer. These methods of rupture assessment have not been validated and are unlikely to detect incidents of silent rupture. Thus, the Kaplan-Meier estimates of rupture within studies which did not use MRI to screen a subset of study participants for rupture may underestimate the incidence of rupture, and studies which did use MRI did not apply this method of follow-up to the full patient cohort. This precludes the comparison of rupture rates between studies and compromises the internal validity of the included studies.

Smooth breast implants have been associated with higher incidences of early capsular contracture compared to textured implants and polyurethane coated (Wong et al 2006); however, the studies included in this rapid review poorly described implant characteristics, limiting any conclusions regarding surface coating and long-term outcomes. A number of studies did not report the surface

of the implant used and outcomes were not reported according to implant surface in any studies. Similarly, earlier generations of implants have been associated with high rates of rupture (Peters et al 1996) and in many of the included studies the generation of the breast implants used could not be ascertained.

Contextual issues

Recently the FDA and the SCENIHR have published reports regarding the safety of silicone and PIP implants. In 2011, the FDA provided a clinical update on the safety of silicone breast implants, and concluded that the safety and effectiveness of silicone-filled implants can be reasonably assured, when used as labelled. However, the report noted that their use is associated with frequent local complications and adverse outcomes. Key local complications and adverse outcomes from silicone gel-filled breast implants were capsular contracture, re-operation, and implant removal. Other local complications included implant rupture, wrinkling, asymmetry, scarring, pain and infection.

The FDA also stated that despite these potential adverse outcomes, the benefits and risks of breast implants are sufficiently understood for women to make informed decisions regarding their usage. How the assessment of patient awareness was garnered is unclear. The report states that surveys of physicians indicate that patients' brochures provided by the manufacturers were useful, informative and effective in communicating breast implant risk.

Extended follow-up of two peer reviewed publications (Cunningham and McCue 2009; Spear et al 2007) were reported in the FDA publication (FDA 2011a). In the extended follow-up high re-operation rates during the first eight to 10 years after implantation were observed. For augmentation patients reoperation was observed to have a range of 20 to 40 per cent and 40 to 70 per cent for reconstruction patients. The ranges of Kaplan-Meier estimates reported by the FDA tended to be higher than those reported at six years (Cunningham and McCue 2009; Spear et al 2007). The FDA further noted that women with breast implants may have a very small but increased risk of ALCL. In contrast, this rapid review concluded that a direct association remains inconclusive based on low level studies, including case series and case reports, and several large epidemiologic cohort studies.

In 2012, the SCENIHR published a report on the safety of PIP silicone breast implants (Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) 2012). The report concluded that irrespective of the manufacturer, silicone breast implants will fail at some point after implantation. The authors also noted that the probability of failure increases with time. A specific focus of the report on PIP implants noted that there were several challenges to an assessment of the risks due to PIP silicone implants including:

- Depending on the country of investigation it was uncertain whether the implant was a PIP implant until explantation.
- Reporting of breast implant failure and adverse events is not obligatory which makes incident rates unreliable.

The report did not document explicit methods for quality appraisal and was limited to a review of silicone filled implants.

Despite the safety concerns of implantation with PIP prostheses, there is inconclusive evidence regarding the comparative safety and device failure risks compared to other implants. Further monitoring and additional information are required to more accurately determine rates of rupture and long term safety outcomes associated with ruptured implants. Consequently, the TGA has not recommended routine removal of PIP implants unless presentation with medical indications, such as rupture or other adverse symptoms. Regardless of manufacturer, all breast implants should be considered high-risk medical devices that carry the risk of rupture or deflation over time, that require monitoring for such complications for the life of the device.

Finally, no studies in this review reported the incidence of rupture or capsular contracture over time. As a result, no conclusions can be drawn regarding the risk of rupture or the in vivo lifespan of breast implants over time. Furthermore, no authors compared the complications and long term outcomes of patients who elected to have their breast prostheses removed; compared to those who suffered rupture and then underwent breast prosthesis removal. Consequently, there is no data to indicate whether outcomes for patients who elect to have breast prostheses removed are superior to those who suffer rupture, and at what time point it is best to screen breast implants for possible rupture or defect. As a result, an area of future research could contribute to the evidence base by documenting the incidence of rupture over time, in order to best formulate a breast prosthesis monitoring program to mitigate against the risk of removal after a rupture has taken place. Collaboration between breast device registries internationally, including congruency with regard to the minimum data set captured, would provide raw incidence data regarding the rate of rupture and capsular contracture over time.

Conclusion

The aim of this rapid review of the literature was to assess the long-term safety and effectiveness of breast implantation for primary and revision breast reconstruction and augmentation; with a particular focus on patient satisfaction, rupture, capsular contracture and wrinkling and rippling. Due to the nature of the available evidence, it was difficult to observe trends in the data. As a result, conclusions which can be drawn are limited by the quality and characteristics of the literature available with duration of follow-up of five years or more. In addition, 17 of the 28 included studies were retrospective in design, making it difficult in some cases to ascertain whether incidences of adverse events or effectiveness outcomes did or did not occur. This combined with poor methods of assessing rupture and determining patient satisfaction presented a challenge for this rapid review.

The majority of the results reported for the safety and effectiveness of breast implantation across all indications was reported as Kaplan-Meier estimates, calculated based on the incidence of safety and effectiveness outcomes in a subset of study participants. Validated tools and structured assessment tools tailored to the outcomes of breast implantation, such as the Breast Q tool were not used to assess patient satisfaction in the included studies. Where reported, patient satisfaction predominantly comprised patient self-assessment using surveys of varying length and content; and only a portion of study participants responded.

As rupture results for all indications were predominantly reported as Kaplan-Meier estimates it is difficult to determine from the literature the long-term incidence of rupture.

Capsular contracture, from both Kaplan-Meier estimates and incidence data, increased over time, particularly between five and 10 and up to 15-year follow-up for all indications and implant types. Silicone gel-filled implants reported the lowest estimate of capsular contracture and wrinkling and rippling in primary reconstruction patients compared to saline-filled and permanent expander implants. In addition, the Kaplan-Meier estimates of adverse events for primary augmentation with silicone gel-filled implants were similar to primary reconstruction patients.

Permanent expanders, used for primary and revision breast reconstruction in three studies, resulted in a higher incidence of adverse events compared to Kaplan-Meier estimates for silicone gel-filled implants for the same indications, and saline-filled implants for primary breast reconstruction. In addition, at 12.5-year follow-up all permanent expanders had been removed (explanted) across the two studies reporting re-operation. Reasons for explantation included capsular contracture, poor aesthetics and deterioration in patient satisfaction.

Overall, as the data presented is primarily comprised of Kaplan-Meier estimates calculated by conducting sub-studies in a subset of patients, determining the in vivo lifespan of breast implants across primary and revision breast reconstruction and augmentation was limited. However, where reported incidence data compared to Kaplan-Meier estimates agreed with the trend in outcomes over time; namely, that capsular contracture, the likelihood of rupture and patient dissatisfaction all increase over time following implantation with any type of breast prostheses.

In addition, the available data suggests re-operation is performed within five to 10 years following implantation due to a variety of reasons ranging from dissatisfaction with style or size of implant, or the occurrence of capsular contracture or implant rupture.

Consequently, developments in the available evidence-base for the assessment of the long-term safety and effectiveness of breast implantation should comprise prospectively designed comparative studies where data is stratified according to surgical technique and the characteristics of the implants used.

Clinical recommendations

The clinical evidence base identified is predominantly low-level evidence that does not contain sufficient clinical data to inform on the long-term safety and effectiveness of breast implantation. Consequently there is a need for data collection in a large number of women, over a long time horizon presenting a higher-level of detail about patient-relevant outcomes than is currently available. It is proposed that industry, government, surgeons and patients all have a role to play in defining and informing on the nature of data that should be collected. The results of this review would support initiatives such as the newly developed Breast Implant Device Registry as well as collaboration across registries internationally to form a consistent minimum data set.

A key outcome of this review could be the generation of a peer reviewed article summarising the current uncertainties around the long-term safety and effectiveness of breast implantation and investigating adjunct areas of clinical uncertainty such as appropriate imaging modalities and screening protocols for implant rupture.

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Appendix A: TGA approved breast prosthesis

ARTG number	ARTG label name
Johnson & Johnson Medical Pty Ltd	
Silicone filled	
110587	Smooth Round Cohesive I - Prosthesis, internal, mammary, gel filled
110588	Siltex Round Cohesive I - Prosthesis, internal, mammary, gel filled
110589	Siltex Round Cohesive II - Prosthesis, internal, mammary, gel filled
130678	Siltex Contour Gel Breast Implants Cohesive III Prosthesis, internal, mammary, gel-filled
160020	PERTHESE Gel Breast Implants - Textured - Prosthesis, internal, mammary, gel-filled
160021	PERTHESE Gel Breast Implants - Smooth - Prosthesis, internal, mammary, gel-filled
162429	Sensitive Gel Breast Implants - Textured - Prosthesis, internal, mammary, gel-filled
Saline filled (inflatable)	
119646	Smooth Saline Mammary Prostheses with Diaphragm Valve - Prosthesis, internal, mammary, inflatable
119718	Smooth Spectrum Post-Op. Adjustable Saline Mammary Implant - Prosthesis, internal, mammary, inflatable
119647	Siltex Saline Mammary Prostheses with Diaphragm Valve - Prosthesis, internal, mammary, inflatable
119719	Siltex Spectrum Post Opt. Adjustable Saline Mammary Implant - Prosthesis, internal, mammary, inflatable
152229	Siltex Round Spectra Adjustable Gel Breast Implants Cohesive I - Prosthesis, mammary, internal, gel/saline-filled, inflatable
152230	Smooth Round Spectra Adjustable Gel Breast Implants Cohesive I - Prosthesis, mammary, internal, gel/saline-filled, inflatable
McGhan & Cui Brand (Silicone filled, saline/silicone filled inflatable)	
126554	single lumen gel-filled breast implants - Prosthesis, internal, mammary, gel-filled
126553	saline-filled breast implants - Prosthesis, internal, mammary, inflatable
126555	breast implants- Prosthesis, mammary, internal, gel/saline-filled, inflatable
Euro Implants Pty Ltd (Silicone filled)	
132040	Cristaline I Aptex/Vertex Paragel Natural Cohesive Gel Implant - Prosthesis, internal, mammary, gel filled
132036	Paragel Cohesive Gel Implant - Prosthesis, internal, mammary, gel filled
132037	Cristaline Paragel Cohesive Gel Implant - Prosthesis, internal, mammary, gel filled
Adirel Consolidated Pty Ltd T/A Surgiplas Medical (Silicone filled, saline filled inflatable)	
142860	Gel Filled Mammary Implant - Prosthesis, internal, mammary, gel filled
142863	Nagor Mammary Implants Gel-filled-TEXTURED - Prosthesis, internal, mammary, gel filled
142861	Nagor Mammary Implants Saline-Filled-TEXTURED - Prosthesis, internal, mammary, inflatable
142862	Saline-Fill Mammary Implant - Prosthesis, internal, mammary, inflatable
Device Technologies Australia Pty Ltd (silicone filled)	
148763	Silicone Gel - Textured Surface - Prosthesis, internal, mammary, gel filled
148764	Silicone Gel-Smooth Surface - Prosthesis, internal, mammary, gel filled
148765	Silicone Gel-Polyurethane Foam Coated - Prosthesis, internal, mammary, gel filled

Medical Vision Australia Plastic & Cosmetic Pty Ltd (Silicon filled)	
165460	CEREFORM Silicone Gel-Filled Breast Implant (Smooth Texture) - Prosthesis, internal, mammary, gel-filled
165461	Silicone Gel-Filled Breast Implant (Intermediate Texture) - Prosthesis, internal, mammary, gel-filled
165462	Silicone Gel-Filled Breast Implant - Prosthesis, internal, mammary, gel-filled
Allergan Australia Pty Ltd (Silicone/saline inflatable, Silicone filled)	
169956	Natrelle Double Lumen Gel/Saline Breast Implants - Prosthesis, mammary, internal, gel/saline-filled, inflatable
171388	Natrelle Saline-filled, Textured Breast Implants - Prosthesis, internal, mammary, inflatable
171387	Natrelle Truform Dual gel, Textured Single Lumen Breast Implants - Prosthesis, internal, mammary, gel-filled
171393	Natrelle Truform1 Gel, Smooth Single Lumen Breast Implants - Prosthesis, internal, mammary, gel-filled
171475	Natrelle Soft Touch, Truform 2 gel, Textured, Single Lumen Breast Implants - Prosthesis, internal, mammary, gel-filled
171512	Natrelle Truform 3 gel, Textured Single Lumen Breast Implants - Prosthesis, internal, mammary, gel-filled
175420	Natrelle Truform1 gel, Textured, Single Lumen Breast Implants - Prosthesis, internal, mammary, gel-filled
175421	Natrelle INSPIRA, Truform 1 gel, Smooth, Single Lumen Breast Implants - Prosthesis, internal, mammary, gel-filled
175422	Natrelle INSPIRA Truform 1 gel, Textured, Single Lumen Breast implants - Prosthesis, internal, mammary, gel-filled
175425	INSPIRA Truform 2 gel, Textured Single lumen Breast Implants - Prosthesis, internal, mammary, gel-filled
175426	Natrelle INSPIRA Truform 2 gel, Smooth, Single Lumen Breast Implants - Prosthesis, internal, mammary, gel-filled
JT Medical Pty Ltd (Silicone filled)	
185060	JT Medical Pty Ltd - 4Two Line, Single Lumen, Micro Polyurethane, Silicone gel filled Mammary Implants - Prosthesis, internal, mammary, gel filled
185059	JT Medical Pty Ltd - 4Two Line, Single Lumen, Textured, Silicone gel filled Mammary Implants - Prosthesis, internal, mammary, gel filled
189780	JT Medical Pty Ltd - Sublime Line, Microthane, Silicone gel filled Mammary Implants - Prosthesis, internal, mammary, gel filled
171782	JT Medical Pty Ltd - Sublime Line, Microthane, Silicone gel filled Mammary Implants - Prosthesis, internal, mammary, gel filled
171781	JT Medical Pty Ltd - Sublime Line, Smooth, Silicone gel filled Mammary Implants - Prosthesis, internal, mammary, gel filled
171783	JT Medical Pty Ltd - Sublime Line, Textured, silicone gel filled Mammary Implants - Prosthesis, internal, mammary, gel filled

Source: TGA (2012a). ARTG: Australian Register of Therapeutic Goods.

Appendix B: Search strategy

#1	Search implant*
#2	Search reconstruct*
#3	Search augment*
#4	Search #1 OR #2 OR #3
#5	Search breast [MeSH Terms]
#6	Search mammar*
#7	Search breast*
#8	Search #5 OR #6 OR #7
#9	Search #4 AND #8
#10	Search breast implants [MeSH Terms]
#11	Search breast implantation [MeSH Terms]
#12	Search breast prosthesis [MeSH Terms]
#13	Search silicone gels [MeSH Terms]
#14	Search #10 OR #11 OR #12 OR #13
#15	Search #9 OR #14
#16	Search #15 Limits: English language, Published 2007 onwards

Appendix C: Excluded studies

Studies excluded on full text review

Follow-up too short or not reported

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