Australian Government

Medical Services Advisory Committee

Public Summary Document

Mentor® textured breast implants and expanders compared with smooth breast implants and expanders on the Prostheses List

Applicant: **Johnson & Johnson Medical Pty Ltd**

Date of MSAC consideration: **MSAC 77th Meeting, 28-29 November 2019**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of submission

The purpose of the submission was to evaluate the safety, effectiveness and cost-effectiveness of Mentor textured breast implants compared with smooth breast implants. Both smooth and textured breast implants appear on the Prostheses List (PL) but with textured implants attracting a higher benefit.

2. MSAC's advice

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support a claim for a higher benefit to be paid for Mentor textured breast implants on the PL compared with smooth breast implants. MSAC considered that there was very limited comparative evidence to inform decision-making about the relative benefits of one type of implant over another for reconstructive surgery, and that the quality of studies comparing textured with smooth implants and the overall evidence base was largely unsatisfactory. MSAC considered the clinical evidence was highly uncertain and that these uncertainties flowed to the economic analysis.

MSAC acknowledged that textured breast implants are preferred by clinicians for use in a small and specific group of women. MSAC noted that retaining the availability of textured breast tissue expanders through listing of the devices on the PL is of particular interest to clinicians.

Consumer summary
Johnson & Johnson Medical Pty Ltd submitted to MSAC that their Mentor brand of micro-textured breast implants should continue to be listed on the Prostheses List and receive a higher level of cost reimbursement than smooth implants.

Consumer summary

Breast implants are funded by private health insurers for use with patients who have a breast reconstruction as a result of cancer, trauma, or a failure of breast development. To be funded by private health insurers the implants must be on the Australian Register of Therapeutic Goods (ARTG - https://www.tga.gov.au/australian-register-therapeutic-goods) and in turn on the Prostheses List (https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-privatehealth-prostheseslist.htm). The surface roughness of breast implants is classified as smooth, micro-textured or macro-textured. Textured breast implants, including micro- and macro-textured, have historically attracted higher benefits than smooth breast implants.

Very rarely, breast implants may be associated with a cancer of the immune system known as breast implant associated anaplastic large cell lymphoma (BIA-ALCL). The association of BIA-ALCL with textured breast implants led to the Therapeutic Goods Administration (TGA), part of the Australian Government Department of Health, decision to remove seven macro-textured and one micro-textured breast implants from the ARTG. The TGA determined that other micro-textured and smooth breast implants could continue to be supplied in Australia with enhanced surveillance for complications including BIA-ALCL.

All breast implants that were removed from the ARTG have also been removed from the Prostheses List. The Mentor micro-textured breast implants continue to be included on the ARTG and Prostheses List.

This submission to MSAC followed the regulatory action taken by the TGA and evaluates whether Mentor micro-textured breast implants should continue to receive a higher level of cost reimbursement than smooth implants. MSAC acknowledges the need to help patients who require a breast reconstruction. However, there are a number of safety concerns associated with the use of breast implants, such as contraction of the capsule surrounding the implant, rupture of the implant and malposition.

MSAC's advice

MSAC advised that the applicant's claim for a higher benefit for its Mentor micro-textured breast implants over smooth breast implants on the Prostheses List was not supported by the clinical evidence provided. MSAC considered that there was very limited comparative evidence to inform decision-making about the relative benefits of one type of implant over another for reconstructive surgery. The quality of studies comparing textured with smooth implants and the overall evidence base was largely unsatisfactory. MSAC acknowledged that textured breast implants and expanders are preferred by some clinicians for use in a small and specific group of women.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that there are Medicare Benefits Schedule (MBS) items for breast prosthesis implantation and removal for breast reconstruction (post-mastectomy for cancer, trauma or agenesis). Breast implant insertion for cosmetic reasons (augmentation) is not subsidised through the MBS and, in turn, the implants used in cosmetic surgery do not attract PL benefits. It was noted that breast reconstruction using breast prosthesis implantation may be a single or two-step procedure, with the two-step procedure involving insertion of a temporary expander followed by the definitive breast implant. MSAC noted that smooth implants dominate in the US, while the majority of implants used in Australia are textured.

MSAC noted that the most common adverse events (AEs) associated with breast implants according to the Australian Breast Device Registry (ABDR) 2016 Annual Report are capsular contracture (39%), device malposition (22%) and device rupture (19%). An AE of particular concern is breast implant associated-anaplastic large cell lymphoma (BIA-ALCL), and that the association of BIA-ALCL with macro-textured implants has resulted in regulatory action by the TGA. MSAC noted that the majority of cases of BIA-ALCL are associated with macro-textured implants but that some had been associated with micro-textured implants.

MSAC noted that the patient population defined in the PICO included both augmentation and reconstruction patients and that capsular contracture was agreed to be the key outcome for the submission. MSAC agreed with the commentary which considered that an area of clinical uncertainty was whether data from patients treated for cosmetic/aesthetic augmentation was applicable given this procedure is not covered by PL or MBS arrangements. In addition, patient risk profiles and surgical pathways are different for patients undergoing augmentation as opposed to reconstruction.

MSAC noted that there are no large, high quality clinical trials of textured versus smooth breast implants for reconstructive patients. One higher quality trial in 20 patients (Thuesen et al. 1995) showed no statistical difference between textured versus smooth implants in the rate of capsular contracture. The applicant submitted in their pre-MSAC response that the choice of breast implants is dependent on each patient's unique circumstances, and that results from randomised control trials (RCTs) may not be generalisable outside the trial setting. The applicant stated that real-world data from larger cohorts with long term follow-up (e.g. from the United States Food and Drug Administration [FDA] 'CORE' studies) is more applicable and was therefore used in the economic model. In particular, long term follow up (10+ years) is required to identify cases of BIA-ALCL.

MSAC noted that a large non-randomised post-approval study with a 10-year follow-up, requested by the FDA, showed a difference between textured and smooth implants in re-operation rates for asymmetry in reconstruction patients (Wixtrom et al. 2019). The applicant proposed in the pre-MSAC response that the ABDR is a potential source of data that would inform the current review. MSAC considered that although the registry data may be useful, there may not be a sufficient sample of smooth implants to properly address current uncertainty because most implants used in Australia are micro-textured.

MSAC noted the following additional areas of clinical uncertainty:

- Whether capsular contracture or other complications is sufficient to assess clinical effectiveness, given there are many other patient-relevant outcomes. The applicant stated in their pre-MSAC response that these have been captured indirectly in re-operation rates in the economic model. MSAC considered this claim to be unfounded.
- Whether the comparison between textured versus smooth implants is confounded by device characteristics, surgical approach and patient/treatment characteristics. The applicant stated in their pre-MSAC response that they recognise there may be confounding factors and that they are likely to have varied across studies, and the variability is representative of 'real world' Australian clinical practice.

In its overall assessment of the available clinical evidence, MSAC considered that there were insufficient comparative data to support a claim that Mentor textured breast implants are clinically superior to smooth implants in reconstructive breast surgery. It considered that the heterogeneity of relevant studies with respect to key characteristics (populations, devices, procedures, follow-up, outcomes) was significant.

MSAC noted the claim from the applicant with respect to the economic evaluation, that Mentor textured implants dominated. The applicant argued that Mentor textured implants were both less expensive (-$1,212) and associated with more quality-adjusted life years (QALYs; 0.001) over the 10-year time horizon compared with smooth breast implants. MSAC considered the areas of economic uncertainty to be:

- Whether inclusion of complication rates from aesthetic augmentation rates was appropriate.
- Whether use of non-comparative data for complication rates was appropriate, given the mix of reconstructive and augmentation patients across the studies, and given there was no difference in complication rates in comparative studies.
- Whether inclusion of reoperation as a health state has the potential for double counting, because reoperation is included as a complication and any double counting would bias the result in favour of textured implants.

While additional analyses were provided by the applicant in their pre-MSAC response regarding the economic uncertainties, MSAC considered that there was a lack of detail provided around these re-analyses.

MSAC noted additional areas of uncertainty with the economic model were:

- Whether omission of discounting is appropriate.
- Whether simplifying assumptions such as direct-to-implant surgery were reasonable.

MSAC considered that the incidence of BIA-ALCL was very low in micro-textured implants and would have little impact on cost-effectiveness compared with other potential complications.

In its overall assessment of the economic evaluation, MSAC considered that the model appeared sensitive to outcomes that are heterogeneous and population dependent (augmentation versus reconstruction), and that double counting with reoperation as a distinct endpoint is an issue. MSAC considered that a simplified approach may be to pool outcomes that would be expected to differ between smooth and textured implants (capsular contracture and malposition) in defined populations (reconstructive patients).

MSAC agreed with the commentary that the available evidence was insufficient to support the applicant's claim of an incremental clinical benefit of Mentor textured breast implants versus smooth breast implants in terms of capsular contracture or any other complication or outcome. MSAC agreed there was very limited comparative evidence to inform decision-making about the relative benefits of one type of implant over another for reconstructive surgery and that the quality of studies comparing textured implants with smooth implants and the overall evidence base was largely unsatisfactory.

MSAC advised that the applicant's claim for a higher benefit for its Mentor textured breast implants over smooth breast implants on the PL is not supported by the evidence provided.

Regarding the question of applicability of the current review to other micro-textured breast implants that are included on the ARTG and listed on the PL, MSAC noted that individual products within a class of implant have been withdrawn, suggesting that product-based reviews with a common template and consensus economic model may be appropriate. MSAC noted that the applicant lodged a submission to support continued listing of their devices.

MSAC considered from the evidence provided that it was difficult to define a reasonable price for the Mentor textured breast implants and that current PL prices do not appear to have been based on economic evaluation but rather transferred from the previous Schedule 5.

MSAC noted that these outcomes have no implications for MBS items for breast reconstructive surgery.

4. Background

In April 2019, the TGA convened its breast implant working group to examine current data on BIA-ALCL rates and correlation with the type of breast implant.

Following a review and laboratory assessment of breast implants and breast tissue expanders sold in Australia, the TGA suspended the supply, import and export of all 'macro-textured' breast implants, and some 'micro-textured' implants associated with higher incidences of BIA-ALCL and "other clinical concerns".

The TGA advised that eight models of textured implants (seven macro-textured and one micro-textured), from four manufacturers were to be suspended from the ARTG for a six-month period which commenced 25 October 2019. The applicant's Mentor textured breast implant devices are 'micro-textured' and continue to be included in the ARTG.

All breast implants that were removed from the ARTG have also been removed from the PL.

New conditions for inclusion in the ARTG have been imposed on ALL breast implant devices that remain available, including tissue expanders:

- All cases of BIA-ALCL must be reported to the TGA by the sponsors within ten days of becoming aware of the adverse event.
- New six monthly reports from sponsors covering supply data and details of all adverse events, and all complaints, both in Australia and world-wide.
- The risk of BIA-ALCL must be included in clinicians' Instructions for Use of all breast implant and tissue expander devices.
- Patient information leaflets must include warnings about the risks of BIA-ALCL.

In addition to these conditions; seven out of ten of the applicant's breast implants are subject to additional clinical data requirements; the applicant must provide the TGA, by 1 July 2020 with:

- Immunotoxicology studies, and
- Updated risk assessment documentation and processes with appropriate hazard controls implemented.

As a result of the association of textured implants and BIA-ALCL, the safety, effectiveness and cost-effectiveness of these devices has been called into question.

Most breast implants listed on the PL have not been subject to a health technology assessment to determine a cost-effective benefit. They were "grandfathered" across from Schedule 5 of the Private Health Insurance Act in 1985.

In July 2019, ahead of TGA's regulatory action, the Department of Health wrote to sponsors of textured breast implants to:

- Request a submission for clinical and cost-effectiveness, given these new findings.
- Request a voluntary "suspension" (deleting and possible subsequent re-listing).

Responses from the sponsors were varied:

- Two sponsors opted for a voluntary suspension. The associated devices have since been removed from the PL.
- One sponsor has had their products removed involuntarily as at least one case of BIA-ALCL has been confirmed.
- The applicant was the only sponsor that responded with a submission to the Department, stating why its Mentor textured breast implant devices should remain on the PL.
- Other sponsors have micro-textured implants that remain on the PL and ARTG but have made no submission.

5. Prerequisites to implementation of any funding advice

The Mentor textured breast implant devices (shown in Table 1) remain registered on the ARTG with additional conditions imposed, as above.

Table 1 Mentor implants listed in the submission

ARTG	Product Name	Description
119809	Mentor Siltex Becker Expander/Mammary Implant	Textured Becker Expander/Mammary Implant
226977	Mentor Siltex Contour Profile Breast Tissue Expander	Siltex Contour Profile Breast Tissue Expander (CPX4)
226982	Mentor Siltex Contour Profile Breast Tissue Expander	Siltex Contour Profile Breast Tissue Expander (CPX4) with suture tabs
110592	Mentor Siltex Round Gel Implant	Textured, Round Cohesive I Gel implant
110589	Mentor Siltex Round Gel Implant	Textured, Round Cohesive Gel II Implant
130678	Mentor Contour Profile Gel Implant	Textured, Contour Profile, Cohesive III, Gel implant

Source: Commentary Appendix A p32

6. Proposal for public funding

This submission did not seek to alter the MBS item descriptor/s in any way.

The focus of the submission was whether the higher benefit payable for Mentor textured breast implants on the PL, compared with smooth breast implants is justified.

7. Summary of public consultation feedback/consumer issues

Three independent clinical experts provided advice to MSAC. The clinicians advised that the use of textured breast implants does have a specific place in the group of women who do not have a tissue-based breast reconstruction, but rather have a saline or gel implant. The experts highlighted the wide variability in how breast reconstructions using breast implants and tissue expanders are performed. While the clinicians acknowledged a real risk and increased diagnosis of BIA-ALCL associated with textured breast implants, they considered the risk to be very small for micro-textured implants in comparison to the benefits provided. It was also considered that the risk of BIA-ALCL in the post-mastectomy due to cancer group may be viewed differently than for other populations. The experts stated that retaining the availability of Mentor textured breast tissue expanders is of particular interest because there are no smooth tissue expanders available, tissue expanders are a temporary measure, and a small group of women would otherwise not be able to have a breast reconstruction.

8. Proposed intervention's place in clinical management

The submission indicated Mentor textured breast implants and tissue expanders are one of several surgical options used in patients undergoing breast reconstruction and breast augmentation. The commentary noted that Mentor textured saline filled implants and tissue expanders are listed on the PL but are not within scope, so the assessment essentially relates to Mentor textured gel filled implants only.

Breast reconstruction
The submission stated patients undergoing primary and revision breast reconstruction who are potentially eligible for treatment with breast implants are within scope of the review. The submission stated the overall category of breast reconstruction surgery includes subcategories involving replacement of missing breast volume in the following situations:

- following mastectomy due to cancer (including prophylactic mastectomy)
- to correct trauma to the breast
- to address congenital deformities, or
- to correct severe breast ptosis.

In addition, breast implants and tissue expanders may be used if there is a need to replace or revise previously reconstructed breasts.

The commentary noted that according to the ABDR Annual Report 2018, of 1593 post-cancer reconstruction procedures involving breast implants, 37% of insertion procedures were direct-to-implant and 63% were two-stage procedures. For risk-reducing reconstruction, the difference was less marked (of 790 procedures, 54% were direct-to-implant and 46% were two-stage). In contrast, 93% (230/247) of breast implant procedures for developmental deformity are direct-to-implant. The staging of insertion procedures and whether breast reconstruction is unilateral or bilateral will have cost implications.

Breast augmentation
The submission stated patients undergoing primary and revision breast augmentation who are potentially eligible for treatment with breast implants are within scope of the review.

However, the commentary considered cosmetic breast augmentation to be out of scope as this procedure is not covered by PL or MBS arrangements, except in the clinically appropriate situations defined in the MBS items. Such MBS services are related to the correction of breast ptosis in the context of breast cancer or developmental abnormality, to match the position of the contralateral breast. Furthermore, due to notable differences in the demographics and health of the patient populations, clinical literature relating to breast augmentation with cosmetic/aesthetic indication is not considered applicable to the reconstruction population eligible for breast implants/expanders on the PL and MBS. If considered at all, data relating to cosmetic breast augmentation should be viewed as supportive evidence at best.

The applicant, in the pre-MSAC response, disagreed claiming data from augmentation populations to be applicable given this review was triggered in response to TGA concerns regarding textured breast implants and BIA-ALCL that were not limited to reconstruction or augmentation patients.

The applicant also claimed that the treatment of complications from augmentation procedures can incur costs to the Australian healthcare system, with implications for Medicare and public hospital budgets. Hence, inclusion of augmentation patients in the submission represents a

more holistic approach to fully understanding the broader implications of the comparative safety of textured versus smooth breast implants.

9. Comparator

The comparator, as amended in the commentary, is breast implantation with smooth implants and expanders (Class-Smooth Implants):

- Saline filled
- Silicone gel filled

- All sizes.

The commentary's preference was to compare the devices to saline filled and gel filled implants separately as they may have a different safety and effectiveness profile.

10. Comparative safety

The submission's literature review identified 47 studies considered eligible for inclusion: 17 meta-analyses; nine systematic reviews; four RCTs; seven Mentor Trials; four FDA reviews; four CORE studies; and two ABDR Reports. The submission stated most of the evidence comparing the efficacy of textured implants will revert to rates of capsular contracture, which was reported as primary outcome for several studies.

Textured versus smooth implants

Capsular contracture

The commentary stated that of the systematic reviews included in the submission only a Cochrane review by Rocco et al. 2016 (n=20) was considered the most applicable study as it compared a cohort of patients who had received implants for breast reconstruction; and Liu et al. 2015, which included a subgroup analysis of the breast reconstruction population (Table 2). The single small RCT identified in the Cochrane review reported two capsular contractures in each arm (Thuesen et al. 1995). Overall, the commentary noted that there are no large, high quality studies of textured versus smooth implants for reconstructive patients. The one valid 1995 trial with n=20 showed rates of capsular contracture of 18.2% versus 22.2% (relative risk [RR] 0.82 [95% CI 0.14, 4.71]) (Thuesen et al. 1995).

Table 2 Summary of systematic literature review and meta-analysis comparing textured and smooth implants for capsular contracture

Paper	Year	Follow up (years)[b]	Population	Intervention (N)	Comparator (N)	Conclusion
Cifuentes et al	2017	nr	Mixed Cohort	Group Texture (1255)	Group Smooth (1047)	Reduced Risk (RR): 0.41 [95% CI 0.31 - 0.54], moderate evidence suggesting that textured breast implants probably reduce the risk of CC
Barnsley et al	2016	8.4	Primary Aug	Group Texture (271)	Group Smooth (261)	Odds Ratio: 0.19 [95% CI 0.07-0.52], CC was 5x more likely with smooth
Barnsley et al	2016	8.4	Primary Aug	Mentor Microtexture (115)	Mentor Smooth (111)	Odds Ratio: 0.06 [95% CI 0.02 -0.16], Mentor Microtexture associated with a statistically significant reduction in CC formation
Rocco et al	2016	3	Primary Recon	Group Texture (11)	Group Smooth (9)	RR: 0.82 [95% CI 0.14 - 4.71], smooth implants were associated with worse outcomes when compared to textured implants for cc
Liu et al	2015	10	Mixed Cohort	Group Smooth (5265)	Group Texture (3193)	RR: 3.10 [95% CI 2.23-4.3]
Liu et al	2015	10	Primary Recon	Group Smooth (na)	Group Texture (na)	RR: 2.3[95% CI 1.17-4.5]
Wong et al	2006	3	Primary Aug	Group Smooth (1 year -209 3 years – 69 7.5 years - 62)	Group Texture (1 year -213 3 years – 79 7.5 years - 72)	1-year RR: 4.16 [95% CI 1.58 - 10.96] p=0.0004 3 years RR: 7.25 [95% CI 2.42 - 21.69] p=0.0004 7 years RR: 2.98 [95% CI, 0.86 to 10.37] p=0.09 Textured implants were associated with less CC

Source: Table 12, p37 of the submission.
Abbreviations: CC=capsular contracture, Primary Aug=Primary Augmentation; Primary Recon=Primary Reconstruction
[b] Mean follow up years where available, otherwise reported as maximum follow up period

No additional relevant RCTs comparing textured implants versus smooth implants were identified in the submission.

The submission also included two non-randomised comparative cohort studies; one comparing textured versus smooth implants (Collis and Sharpe 2000) and one comparing Mentor textured versus other textured implants (Doren et al. 2015). The commentary identified two additional comparative cohort studies comparing textured versus smooth implants (Antony et al. 2014) and the other comparing Mentor textured versus other textured

implants (Microcell) (Benediktsson and Perbeck 2006). The commentary stated there was no difference between textured and smooth implants for capsular contracture:

- Collis and Sharpe (2000) series of 189 two-stage breast reconstructions (1986-1998), capsular contracture 8.4% textured versus 12.8% smooth, unadjusted RR 0.68 [95% CI 0.28, 1.7]. See Table 3 below.
- Antony et al. (2014) series of 365 two-stage breast reconstructions (1997-2007), capsular contracture significant in univariate analysis but not at multivariate analysis. Overall rate of 8.4%.

Table 3 Textured vs. smooth implants for capsular contracture, Collis and Sharpe (2000)

Textured				**Smooth**			
Implant type	**N patients/ breasts**	**N contracture**	**CC Grade (III/IV)**	**Implant type**	**N patients/ breasts**	**N contracture**	**CC Grade (III/IV)**
Mentor textured	66	5	8	Other Smooth (Nagor)	75	10	13
Mentor textured Becker	17	2	12	Dow Corning smooth	11	1	8
Total textured	**83**	**7**	**8.4% (3.9-16.7)**	**Total smooth**	**86**	**11**	**12.8% (7.1-21.6)**

Source: Table 4, p13 of the commentary
Abbreviations: CC, capsular contracture.

The submission also included outcomes for textured versus smooth implants from FDA requested studies:

- Spear and Murphy (2014) included 98 reconstructions patients. No difference between textured and smooth implants in 10-year Kaplan-Meier rates of capsular contracture for Allergan Natrelle implants (23.7% [95% CI 13.9, 38.6] versus 25.8% [95% CI 12.9, 47.5]).
- Wixtrom et al. (2019) reported on 552 primary augmentation and 251 primary reconstruction patients using the Mentor MemoryGel implants.
    - No difference between textured and smooth implants in 10-year Kaplan-Meier rates of capsular contracture for sub-muscular placement in augmentation patients.
    - Significant difference between textured and smooth implants in 10-year Kaplan-Meier rates of capsular contracture for sub-glandular placement in augmentation patients.

Other safety outcomes

A single study which aimed to compare breast implant deflation for anterior and posterior valve placement was included in the submission (Levi et al. 2008). In multivariate analysis, the risk of rupture using a smooth implant was 1.25 higher than with a textured (Siltex) implant, this did not reach statistical significance (p = 0.71). As they were saline filled this study is of lower applicability.

Of the FDA requested studies included in the submission, Wixtrom et al. (2019) reported a difference in reoperation over 10 years for asymmetry with textured (3.88% [95% CI 1.63, 9.13]) versus smooth implants (11.10% [95% CI 6.29, 19.19]; p=0.0169). The overall

reoperation rate is not reported, and whether this differs by texture, was also not reported p=0.0169).

The submission briefly discussed comparative evidence related to safety outcomes for infection, reoperation rate, seroma and rupture. For these safety outcomes, the submission suggested that the Mentor textured breast implants are comparable to smooth breast implants.

In regards to BIA-ALCL, the submission did not compare the safety of the Mentor textured implants to smooth breast implants. However, the submission suggested that the clinical benefits of textured breast implants, a significant lowering of certain complications, and more importantly subsequent reoperations might provide significant risk reduction benefits to offset the rare risk of BIA-ALCL associated with Mentor textured breast implants.

Textured versus other textured implants

Capsular contracture

The submission also provided supportive evidence of Mentor textured versus other brands of textured implants. The commentary noted this comparison was not specified in the agreed PICO, but included results of this comparison from two studies (Table 4).

Table 4 Capsular contracture rates for Mentor textured implants versus other textured implants

Paper	Implant type	N patients/breasts	N contracture	CC Grade (III/IV)
Doren et al. (2015)	Mentor Microtextured	38	4	10.5% (2.9, 24.8)
	Other textured (Allergan)	60	6	10.0% (3.8, 20.5)
	Other textured (Sientra)	15	2	13.3% (1.7, 40.5)
Benediktsson and Perbeck (2006)	Mentor Microtextured	62	8	12.9% (5.7, 23.9)
	Other textured (Microcell)	45	14	31.1% (18.1, 46.7)

Source: Table 5, p14 of the commentary
Abbreviations: CC=capsular contracture.

Other safety outcomes

The commentary included data for other complications in the comparison of different types of textured implants (Table 5).

Table 5 Complication rates of Mentor textured implants versus other textured implants (Doren et al. 2015)

Complication	Mentor Microtextured	Other textured (Allergan)	Other textured (Sientra)
Patients/ breasts, N	38	60	15
Reoperation, N (%)	17 (44.7)	36 (61.0)	8 (53.3)
Explantation, N (%)	1 (2.6)	7 (11.7)	3 (20.0)
Hematoma, N (%)	0 (0.0)	1 (1.7)	0 (0.0)
Rupture, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Asymmetry, N (%)	5 (13.2)	14 (23.3)	5 (35.7)

Source: Table 6, p14 of the commentary

Single-arm evidence

The submission also presented a number of case series studies (Table 6). The commentary included one additional study (Salzberg et al. 2016; highlighted in below table); however, noted the evidence derived from these studies is low level and unsuitable for consideration given the inability to compare across studies due to the many other differences likely to affect rates of capsular contracture and other complications such as follow-up, surgical technique,

device characteristics (fill, shape), treatment (radiotherapy, chemotherapy), patient characteristics etc.

Table 6 Summary of capsular contracture from single-arm studies of textured and smooth implants in reconstruction patients

First author	Follow up (mean years)	Population	N patients/ breasts	N contracture	Implant type	CC Grade (III/IV)
Textured						
Hammond et al. (2017)	10*	Primary Recon	190	NR	Mentor Microtextured	14.3% [a]
Pukancsik et al. (2017)	1.95	Primary Recon (single step)	102	2	Mentor Microtextured	1.2%
Hammond et al. (2017)	10*	Revision Recon	69	NR	Mentor Microtextured	16.4% [a]
Smooth						
Azzi, Zammit, and Lessard (2018)	6.8	Primary Recon (single step)	105	5[b]	Mentor Smooth	4.8%
Becker, Lind, and Hopkins (2015)	2	Primary Recon	31	2[c]	Mentor Smooth	6.5%
Eberlin, Gfrerer, and Liao (2014)	1.5	Primary Recon	16	NR	Mentor Smooth	0%
Lessard (2009)	NR	Primary Recon	44	NR	Mentor Smooth	0.15%
Zienowicz and Karacaoglu (2007)	1.5	Primary Recon	24		Mentor Smooth	0%
Salzberg et al. (2016)	4.7	Primary Recon	863/1584	9/12	Smooth (1529 implants) Textured (55 implants)	1.0%

Source: Table 7, p15 of the commentary
Abbreviations: CC, capsular contracture; NR, not reported; Recon, reconstruction.
Notes: study shaded green was not included in the submission but identified during preparation of the commentary
* maximum follow-up
a Kaplan-Meier estimated cumulative incidence rates
b Capsular contracture requiring reoperation, not according to Baker grade (i.e. likely more severe cases, and therefore an underestimate)
c Grade of capsular contracture not defined

Observational data

The submission also reported revision rates and issues identified at revision from the ABDR. The commentary noted the following ABDR data as relevant to the current submission:

- Use of smooth round silicone implants for reconstructions appears to be increasing from 20.8% in 2012-2017 (2,427 implants) to 30.3% in 2018 (1,132 implants).
- Increasing use of acellular dermal/synthetic matrices, used in 51% of direct-to-implant insertions for post cancer reconstruction and 58% of risk-reducing reconstructions. These are associated with very low rates of capsular contracture (for example, Unger and Keller 2019).
- Top three issues identified at revision of reconstructive breast implants (2018):
    - capsular contracture (n=498, 39.1%)
    - device malposition (n=424, 33.3.%)
    - device rupture (n=215, 16.9%).

The commentary acknowledged data from the ABDR may be useful to identify potential differences in revision rates, or reasons for revision, for textured versus smooth implants in reconstruction. Between 2012-2018, 5,834 reconstruction revision procedures have been recorded. However, the commentary stated the observational breast reconstruction data showed no convincing difference between textured and smooth implants for any outcome.

11. Comparative effectiveness

The submission's comparative effectiveness was considered in terms of safety via reduced complications (discussed above in section 10).

The commentary questioned whether capsular contracture and other complications from breast implants and breast tissue expanders are sufficient to assess clinical effectiveness, given that patient-relevant outcomes include breast appearance, nipple sensation changes, breast sensation changes, and health-related quality of life (patient satisfaction, body image, self-esteem, return to work/family caring). Very little comparative information is available in regard to these patient-relevant outcomes as they are not widely collected and are poorly reported in the literature. Unsatisfactory breast appearance and asymmetry are common reasons for reoperation, but reoperation rates also capture other complications and biopsy for breast masses.

Clinical claim
The clinical claim in the submission was:

- Mentor textured breast implants are superior to smooth breast implants in terms of reducing capsular contracture.

The submission made no other clinical claims. The higher relative benefit on the PL for textured implants therefore relies on the availability of evidence to demonstrate that rates of capsular contracture are lower for textured breast implants compared with smooth breast implants.

12. Economic evaluation

The submission presented a cost-utility analysis (decision tree) comparing Mentor textured implants versus:

- Smooth breast implants
- Other textured implants
- Combination of smooth and or textured implants (Table 7).

The commentary noted that the Mentor textured implant, at $1,170 on the July 2019 PL Part A, is $575 per implant more expensive than the smooth implant, which is listed at $595.

The commentary noted in terms of assessing this additional cost, Criterion 5 of the Prostheses List guidance advises that cost should be relative to its clinical effectiveness. In the submission's model, clinical effectiveness was considered in terms of safety via reduced complications. This appears consistent with other economic evaluations in this area, albeit from settings outside Australia. The commentary did not perform additional modelled scenario analysis due to the uncertainty regarding the comparative clinical evidence.

Table 7 Key components of the economic evaluation

Component	Description	
Type of analysis	Cost-utility	
Outcomes	Quality-adjusted life-years	
Time horizon	10 years	
Method(s) used to generate results	Decision Tree Analysis	
Terminal nodes	• Successful surgery • Implant rupture • Hematoma • Seroma	• Reoperation • BIA-ALCL • Infection • Capsular contracture (Baker class III or IV)
Model probabilities and utilities	Primary data sources: Hammond et al. (2017); Calobrace et al. (2017); Collett et al. (2019); Krishnan et al. (2014); Collins and Verheyden (2012); Maxwell et al. (2012)	
Software	Excel 2016	
Discount rate	0%	

Source: Table 8, p19 of the commentary
Abbreviations: BIA-ALCL=breast implant-associated anaplastic large cell lymphoma.

Modelling assumptions

The submission assumed all complications occur at some time during the 10-year time horizon, to have a duration of one month, to be mutually exclusive, to occur once only and to be resolved following the one-month duration. The complement of the sum of probabilities for complications was assigned as a 'successful surgery' health state. During the complication, a reduced utility value was assigned, with the utility value returning to that of 'successful surgery' after one month. All procedures were assumed to be one-stage (e.g. mastectomy and implant fitting in the same procedure).

The commentary noted that several simplifying assumptions have been introduced in conducting the economic evaluation. The assumption of one-stage implantation does not seem consistent with the ABDR data, with 63% (n=1,593) of post-cancer reconstruction procedures in 2018 implanted as a two-stage procedure (i.e. expander, followed by subsequent reoperation to fit a breast implant). This would make a difference if complication rates were different between implant types based on one-stage or two-stage procedures. The inclusion of breast tissue expanders within scope for the review would also indicate that more thorough discussion of any differences between one- and two-stage insertions would aid interpretation.

Results of the economic evaluation

In the submission's economic evaluation, Mentor textured implants dominated, that is that they are both less expensive and associated with more QALYs over the 10-year time horizon, compared with smooth implants (Table 8). This finding was the same when comparing with other textured, or textured or smooth implants.

Table 8 Overview of base-case cost-utility analysis results for intervention (Mentor textured) versus three comparators (smooth, other textured, smooth or other textured)

	Mentor textured	Smooth	Other textured*	Smooth or other textured*
Expected cost per individual	$redacted	$redacted	$redacted	$redacted
Expected QALYs per individual	redacted	redacted	redacted	redacted
Incremental cost per individual		$redacted	$redacted	$redacted
Incremental QALYs per individual		redacted	redacted	redacted
Incremental cost per QALY gained		**redacted**	**redacted**	**redacted**
Net monetary benefit#		**$redacted**	**$redacted**	**$redacted**

Source: Table 13, p 27 of the commentary

Abbreviations: QALY=quality-adjusted life year.

*Incremental values refer to Mentor textured versus the comparator.

A positive net monetary benefit indicates cost-utility at the willingness-to-pay value of $45,000.

One-way sensitivity analysis

The results of the one-way sensitivity analysis were provided in the submission (shown below Figure 1). The components having the most effect on the net monetary benefit (NMB) were: probability of reoperation; probability of capsular contracture with smooth implants; probability of smooth implant rupture; and the cost of the Mentor textured implant. None of the one-way sensitivity analysis values indicated a negative NMB. A negative NMB would indicate the intervention is not cost-effective at the willingness-to-pay threshold of $45,000.

Figure **redacted**

The commentary queried the economic model regarding whether the:

- Inclusion of complication rates from aesthetic augmentation populations is appropriate, given there are fundamental differences between aesthetic and reconstructive indications in terms of patient risk profile and surgical pathways.
- Use of non-comparative data on complication rates is appropriate given that the mix of reconstructive and augmentation patients is inconsistent across studies and differences in complications between textured and smooth implants are not observed in comparative studies.
- Inclusion of reoperation as a health state has the potential for double counting.

In the pre-MSAC response the applicant provided additional analysis (Table 9) that explored the impact of:

- removing complication rates from aesthetic augmentation populations (scenario analysis 1)
- primary reconstruction patients only (scenario analysis 2)
- excluding re-operation from the economic model (scenario analysis 3).

The applicant claimed that the results of the additional analyses show that Mentor textured implants are cost-effective in comparison to smooth implants.

Table 9 Additional scenario analyses comparing Mentor textured and smooth breast implants

Scenario	Net Monetary Benefit[1]
1. Modelling includes only redacted as per the original model while other complications are set to 0%: comparing Mentor Textured versus Other Smooth, augmentation & reconstruction patients as per OHTA accepted PICO	$redacted
2. Modelling includes only redacted for primary reconstruction patient population only- sourced from Wixtrom 2019 et al (Mentor Textured versus Mentor Smooth: 3.88% versus 11.10%)	$redacted
3. Modelling excludes re-operation in both arms; – Mentor Textured versus Other Smooth (remaining complication data points remains unchanged as per the original model), augmentation & reconstruction patients as per OHTA accepted PICO	$redacted

Source: Applicant pre-MSAC response p6
Abbreviations: PICO=Patients Intervention, Comparator, Outcomes; OHTA=Office of Health Technology Assessment.
[1]Positive net monetary benefit indicates that the intervention is cost-effective where the willingness-to-pay threshold is AU $45,000 per QALY.

13. Applicant's comments on MSAC's Public Summary Document

Johnson & Johnson Medical (JJM) thanks MSAC for their time in evaluating this submission. In support of clinicians and patients, we remain committed to ensuring access to Mentor textured breast implants of which safety and performance has been deemed acceptable by the TGA. We acknowledge MSAC's advice with regards to the scope of the review, however are concerned that this assessment is not an optimal approach to address the Office of Health Technology Assessment's PLAC Criteria 5 of the Prostheses List. We are of the opinion, in light of this with no formal PICO agreement, that this could unintentionally disadvantage JJM. As a result of this, JJM are concerned that there may be unintended consequences for patient and surgeon access to Mentor textured implants. MSAC has noted there are limitations to comparative clinical evidence which flows into the economic modelling. This assessment highlights the challenge to inform decision-making about the relative benefits of one type of permanent gel implant vs another for breast reconstructive surgery. The reality within the Prostheses List processes is, any change to the current reimbursement arrangements requires ongoing consultation with JJM, taking into account MSAC's advise to PLAC, and clinical experts' interest in retaining the availability of temporary textured expanders.

14. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website