Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1541 – Micro-bypass glaucoma surgery device implantation as a standalone procedure in patients with open angle glaucoma

Applicant: **Australian and New Zealand Glaucoma Society and the Royal Australian & New Zealand College of Ophthalmologists**

Date of MSAC consideration: **MSAC 74th Meeting, 22-23 November 2018**

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

1. Purpose of application

An application requesting Medicare Benefit Schedule (MBS) listing for trabecular micro-bypass glaucoma surgery and suprachoroidal micro-invasive glaucoma surgery using stent implantation in the standalone population (i.e. not in conjunction with cataract surgery) was received from the Australian and New Zealand Glaucoma Society (ANZGS) and the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC did not support public funding for micro-bypass glaucoma surgery (MBGS) device implantation as a standalone procedure in patients with open angle glaucoma (OAG). MSAC considered that patient population and eligibility criteria were poorly defined with uncertain comparative safety, clinical effectiveness and cost-effectiveness.

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

MSAC noted that Application 1541 is a submission for reconsideration of a previously unsuccessful component of Applications 1483 and 1496 for micro-invasive glaucoma surgery (MIGS). MSAC recalled that, in November 2017, it had recommended trabecular MIGS (TB MIGS) and suprachoroidal MIGS (SC MIGS) performed in conjunction with cataract surgery. However, it had not supported MIGS as a standalone procedure due to insufficient evidence of effectiveness and because the population who would be eligible for the service could not be adequately defined. The MSAC Executive had determined that a resubmission for the standalone procedure could be considered in a fit-for-purpose pathway and the PICO did not need to be assessed by PASC.

MSAC noted that the application included poorly defined eligibility criteria and patient population, with the potential for leakage.

MSAC expressed concern about the application's claim that MBGS was potentially inferior to trabeculectomy in terms of comparative effectiveness, but superior in terms of comparative safety. MSAC considered that both claims were highly uncertain.

MSAC had several concerns about the economic evaluation and costs. The application put forward a cost analysis, which is inappropriate for the clinical claim of inferior effectiveness and superior safety. A cost-utility analysis would have better informed MSAC decision-making.

MSAC was also concerned about recent safety issues. In August 2018, Alcon recommended an immediate, voluntary market withdrawal of its product SC MBGS CyPass Micro-Stent from the global market, advising surgeons to immediately cease further implantation of the stent and to return any unused devices to Alcon. **Redacted**.

MSAC noted that some of the clinical evidence from the initial submission was from SC MBGS (CyPass) as opposed to TB MBGS (iStent). The previous application separated these two products, but the current submission groups them together as MBGS. Hence, MSAC was concerned that it could not rely on the evidence presented, due to the safety concerns regarding CyPass. MSAC also noted that there were no high-quality randomised controlled trials on which to base decision-making for MBGS.

MSAC evaluated evidence for clinical effectiveness, cost-effectiveness and safety of MBGS within the parameters defined in the agreed PICO confirmation. During consideration, MSAC also discussed if the comparator presented – trabeculectomy (incision therapy) – was appropriate, and if continued topical medical therapy (eye drops) might be an appropriate comparator. The clinical effectiveness of topical medical therapy, and of incisional surgery compared with topical medical therapy, are unknown. MSAC noted a trial comparing the effectiveness of incisional surgery with topical medical drop therapy is currently recruiting until 2020, with results not expected for several years.

MSAC considered that intraocular pressure (IOP) as an endpoint may not be appropriate, as IOP is a surrogate endpoint to predict clinically relevant outcomes such as vision loss and quality of life (QoL). Elevated IOP is a risk factor for the development and progression of glaucoma, and predictive of future visual field loss, but is not the only risk factor and predictor.

The Department suggested a cost of $300 per implantation; the application states $700 per implantation. In addition, patients may require hypotensive medicines following MBGS implantation. This affects the economic evaluation and creates uncertainties in ongoing costs and financial impact. MSAC also considered that there is no data regarding failure rates of MBGS devices, and the need or not for replacement.

MSAC acknowledged the varied support from the ophthalmology community for MBGS, and that consumer organisation claims of unparalleled safety and advanced technology however, they are not supported by clinical trial data.

MSAC concluded that MBGS may offer a very small potential cost saving for the health system compared with trabeculectomy, but these savings are sensitive to several uncertainties, including the number of follow-up visits, adverse events and the possibility of device failure or dislodgement. MSAC also acknowledged the concern about long-term safety

for at least one device and recommended that advice be sought from TGA about the implications for other devices. MSAC suggested that the applicant and other stakeholders with an interest in the outcomes of the Public Summary Document (PSD) may require a meeting to discuss the reasons leading to the decision not to recommend the service for public funding.

4. Background

In November 2017, the MSAC recommended the listing of TB MIGS and SC MIGS on the MBS (MSAC Applications 1483 and 1496, respectively) for patients with OAG undergoing concomitant cataract surgery. Whilst the applications were under consideration, MIGS services performed in conjunction with cataract surgery were allocated an interim item number (MBS item 42705); this has since become an ongoing MBS listing taking effect on 1 November 2018. There is no MBS item for MIGS not performed in conjunction with cataract surgery.

MSAC did not support TB MIGS and SC MIGS as a standalone procedure due to insufficient evidence of effectiveness and because the population who would be eligible for the service could not be adequately defined.

5. Prerequisites to implementation of any funding advice

Australian Register of Therapeutic Goods (ARTG) listings that are relevant to this application are provided in Table 1.

Table 1 Items relevant to the proposed MBS service listed on the ARTG

ARTG no.	Product no.	Product description	GMDN	Product category	Sponsor	Intended purpose
219246	GTS100L GTS100R	iStent trabecular micro-bypass stent system	61127 Glaucoma shunt	Medical Device Class III	RQSolutions Medical Devices Distribution Support *	The iStent Trabecular Micro-Bypass System is intended to reduce intraocular pressure in adult patients diagnosed with mild to moderate primary open-angle glaucoma (POAG) currently treated with ocular hypotensive medication. The device can be implanted with or without cataract surgery.
250914	G2-M-IS AS.	iStent Inject trabecular micro bypass system	61127 Glaucoma shunt	Medical Device Class III	RQSolutions Medical Devices Distribution Support *	The iStent inject Trabecular Micro-Bypass System is intended to reduce intraocular pressure in adult patients diagnosed with mild to moderate primary open-angle glaucoma (POAG) currently treated with ocular hypotensive medication. The device can be implanted with or without cataract surgery.
301403**	N/A	Hydrus microstent	62945 Glaucoma micro-stent	Medical Device Class IIb	Emergo Asia Pacific Pty Ltd T/a Emergo Australia	The Hydrus Microstent is intended for the reduction of intraocular pressure (IOP) in patients with primary open angle glaucoma (POAG) as a standalone treatment or in conjunction with cataract surgery.
163624	N/A	CyPass System	61127 Glaucoma shunt	Medical Device Class IIb	Alcon Laboratories Australia Pty Ltd	The device is intended for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma; and for use in conjunction with cataract surgery or in a standalone procedure for the reduction of IOP in adult patients with primary open-angle glaucoma where previous medical treatments have failed.

Source: Therapeutic Goods Administration (https://www.tga.gov.au/australian-register-therapeutic-goods); accessed 29 May 2018
* RQSolutions is the nominated TGA sponsor and holds the registration on behalf of Glaukos Corporation, with a wholly owned subsidiary Glaukos Australia Pty Ltd conducting business in Australia.
** This reflects recent updates to the ARTG listing for Hydrus Microstent, effective 29/3/2018. The superseded ARTG listing is 212194.

6. Proposal for public funding

The wording of the item descriptor for MBGS stent implantation as a standalone procedure has been revised to more adequately define the patient population who would meet eligibility for the intervention in clinical practice. The proposed MBS item descriptor (Table 2) and proposed alternative MBS item descriptor (Table 3) were based on MBS item 42746 and MBS item 42705, respectively.

Table 2 Proposed MBS item descriptor for MGBS stent implantation

Category 3 – THERAPEUTIC PROCEDURES
MBS item number GLAUCOMA, implantation of, a micro-bypass glaucoma surgery stent system into the trabecular meshwork/suprachoroidal space, in patients diagnosed with open-angle glaucoma, where conservative therapies have failed, are likely to fail, or are contraindicated. Multiple Services Rule (Anaes.) (Assist.) **Fee:** $699.45 **Benefit**: 75% = $524.60

Table 3 Proposed alternative MBS item descriptor for MGBS stent implantation

Category 3 – THERAPEUTIC PROCEDURES
MBS item number GLAUCOMA, implantation of, a micro-bypass glaucoma surgery stent system into the trabecular meshwork/suprachoroidal space, in a patient diagnosed with open-angle glaucoma, who is not adequately responsive to topical anti-glaucoma medications or who is intolerant of anti-glaucoma medication. Multiple Services Rule (Anaes.) (Assist.) **Fee:** $699.45 **Benefit**: 75% = $524.60

As per the previous submissions (i.e. MSAC 1483 and 1496), an item descriptor was proposed in the resubmission for MGBS stent removal (Table 4).

Table 4 Proposed MBS item descriptor for MGBS stent removal

Category 3 – THERAPEUTIC PROCEDURES
MBS item number GLAUCOMA, removal of a micro-bypass glaucoma surgery stent system from the trabecular meshwork/suprachoroidal space. Multiple Services Rule (Anaes.) **Fee: [Fee to be determined]**

For Applications 1483 and 1496 (PSD Applications 1483 and 1496, page 1), MSAC recommended the item at a fee of $300.75 for stent removal regardless of whether it is undertaken with or without stent replacement. The resubmission stated that the recommended item descriptor would therefore also be relevant to the removal of a MBGS device in the current context, i.e., regardless of whether stent implantation was performed as a standalone procedure or in conjunction with cataract surgery.

7. Summary of Public Consultation Feedback/Consumer Issues

Letters of support for MBS funding of MGBS were provided by two professional organisations and one consumer organisation.

8. Proposed intervention's place in clinical management

The clinical management algorithm, which was adapted from relevant clinical guidelines (ANZGS Guidelines, 2018; National Health and Medical Research Council (NHMRC) Glaucoma Guidelines, 2010), depicts the intended use of MBGS implantation (highlighted

red) as a standalone procedure within the current OAG treatment pathway. Specifically, MBGS is expected to be provided as a substitute and/or in addition to other second-line treatment options for patients with OAG (Figure 1), noting that patients can undergo an MBGS standalone procedure following trabeculectomy or further incisional surgery/aqueous tube shunt implantation.

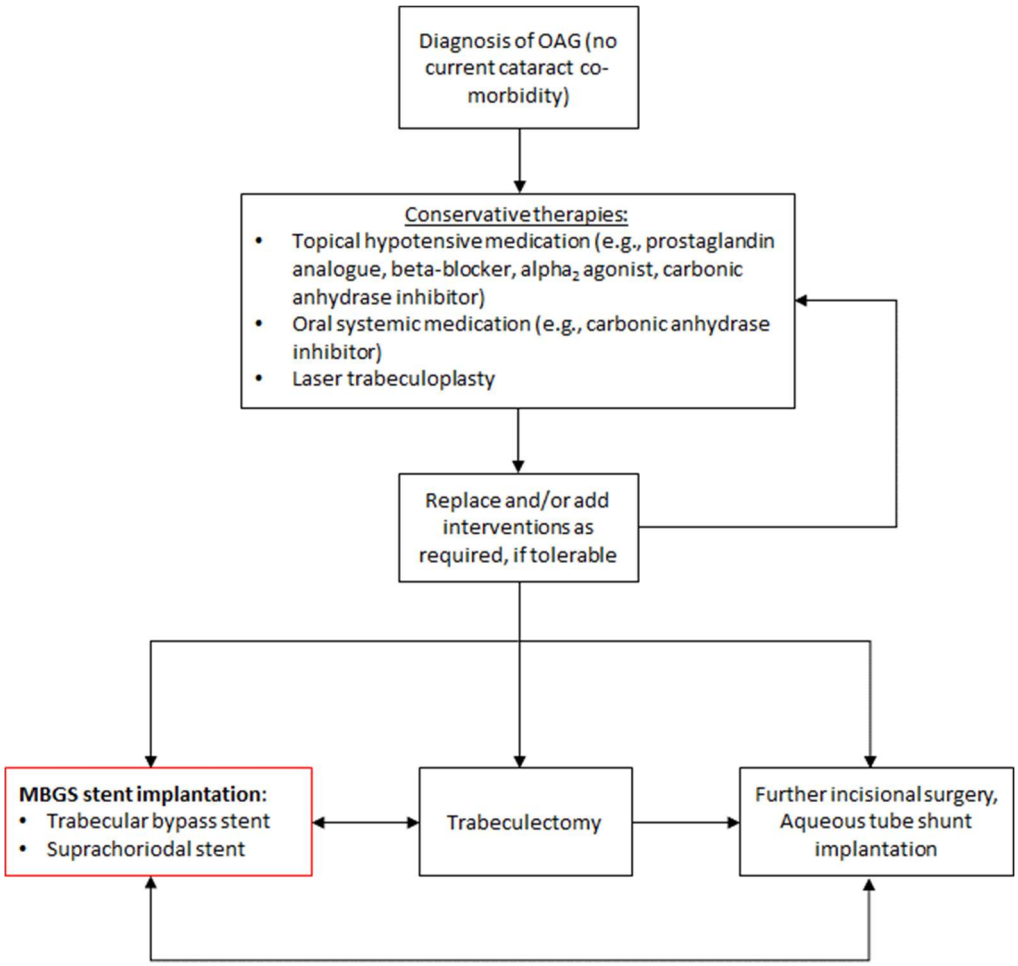

Figure 1 **Clinical management algorithm for trabecular bypass MBGS stent implantation in the standalone patient population, as it fits into the current treatment algorithm**

9. Comparator

The proposed comparator to MBGS is trabeculectomy, a common incisional surgical procedure for OAG. The resubmission stated that the decision to undertake MBGS stent implantation as a standalone procedure will be made on the basis of a favourable risk versus benefit profile of MBGS relative to alternative incisional surgical procedures such as trabeculectomy when conservative first-line therapies have failed, are likely to fail or are contraindicated.

10. Comparative safety

No head-to-head randomised controlled trials (RCTs) were identified comparing MBGS stent implantation versus trabeculectomy. The SBA (resubmission) presented a naïve indirect comparison, consisting of two RCTs (3 publications) and 11 non-randomised studies (12 publications) of MBGS in the standalone setting, together with a systematic review including a meta-analysis of trabeculectomy and a UK National Trabeculectomy Survey.

Relative to trabeculectomy, MBGS stent implantation demonstrates a different profile of potential adverse events consistent with the less invasive nature of the procedure. MBGS reported any surgical complications in 3.2 to 3.7% of procedures whereas the RCTs for trabeculectomy reported event rates for a number of single events of over 10% (Collaborative Initial Treatment of Glaucoma Study (CIGTS)) and the UK National Survey reported event rates of 20% (Table 5).

Table 5 Summary of adverse events across the trabeculectomy and MBGS studies

	CIGTS	UK National Survey	MBGS
Adverse event	**N= 517**	**N=1240**	
Any			
Surgical complications[3]			3.2 to 3.7%
Early complications			
Hyphaema	54 (10.4%)	304 (24.6%)	1.3 to 6.2%
Shallow/flat anterior chamber	73 (14.1%)	299 (24.1%)	
Hypotony		296 (24.3%)	0.0 to 2.6%
Bleb leak		216 (17.6%)	
Choroidal detachment	58 (11.2%)	175 (14.1%)	
Malignant glaucoma		2 (0.2%)	
Endophthalmitis (early)		1 (0.1%)	
Late complications			
Cataract		251 (20.2%)	29.6% (5 years)
Encapsulated belb	61 (11.8%)	42 (3.4%)	
Ptosis	61 (11.8%)		
Endophthalmitis (late)		3 (0.2)	

The resubmission stated that despite the lack of formal statistical comparison, this summary shows MBGS to be superior to trabeculectomy in the incidence of surgical complications and other adverse effects.

11. Comparative effectiveness

The resubmission claimed that the standalone MBGS procedure was associated with a reduction in intraocular pressure (IOP) as well as a reduced need for ocular hypotensive therapy. The reduction in IOP was maintained until 5 years post implantation. Efficacy outcomes for trabeculectomy versus medical therapy reported in the included systematic review (Burr 2012) showed trabeculectomy to be associated with a significantly greater mean change in IOP from baseline compared to medical therapy. On the basis of this single outcome, the SBA (resubmission) claimed that trabeculectomy is likely to be superior to MBGS standalone procedure in terms of comparative effectiveness.

Clinical Claim

The resubmission stated that based on an assessment of clinical evidence of MBGS stent implantation versus trabeculectomy, MBGS is likely to be:

- Potentially inferior to trabeculectomy in terms of comparative effectiveness; and
- Superior in terms of comparative safety.

12. Economic evaluation

The economic evaluation was a cost-analysis of MBGS compared to trabeculectomy (Table 6).

Table 6 Summary of the economic evaluation

Perspective	Australian health care system
Comparator	Trabeculectomy procedure
Type of economic evaluation	Cost analysis
Sources of evidence	Clinical evidence presented in Section B.6
Time horizon	Not specified
Outcomes	Not specified
Methods used to generate results	Cost analysis
Discount rate	Not specified
Software packages used	Microsoft Excel®

Before accounting for adverse events, a single MBGS procedure is estimated to cost $3,564.20 per eye compared to $4,311.59 for trabeculectomy. A single MBGS procedure was estimated to accrue adverse event costs of $34.82 compared to $139.95 for trabeculectomy. The cost analysis, including the costs of the respective procedures, the costs of managing adverse events, and the costs associated with any subsequent procedures (e.g. trabeculectomy due to treatment failure) is summarised in Table 7.

Table 7 Cost analysis comparing MBGS versus trabeculectomy

Parameter	MBGS	Trab	Difference	Reference
Total cost per initial procedure	$3,599.02	$4,451.54	-$852.52	Sum of hospital admission, professional services, prosthesis, post-op consultations and adverse events
Patients requiring subsequent trabeculectomy due to treatment failure	17% (11/64)	0%	-13.3%	Section C based on the DUETTE study Assumed 0% for trabeculectomy arm
Expected total cost of subsequent trabeculectomy	$765.11	$0.00	$765.11	$4451.54 x 17%
Total cost per patient	$4,364.13	$4,451.54	-$87.41	Sum of initial procedure and repeat trab.

13. Financial/budgetary impacts

An updated budget impact analysis was presented in this resubmission using an epidemiological approach to estimate the size of the population eligible for MBGS implantation (in either the cataract or stand-alone settings).

The financial implications to Government and non-Government health budgets from the proposed MBS listing of MBGS stent implantation are summarised in Table 8 .

Table 8 Net budget impact of MBGS listing on public and private healthcare

Service/Budget	2019	2020	2021	2022	2023
Service utilisation					
Total MBGS	11,944	12,224	12,500	12,780	13,072
CS setting	10,750	9,779	8,750	7,668	6,536
Standalone setting	1,194	2,445	3,750	5,112	6,536
MBS perspective					
Cost of the service to the MBS	$3,446,284	$3,847,713	$4,262,237	$4,692,967	$5,143,002
Substituted laser trabeculoplasty[a]	-$1,309,194	-$1,191,008	-$1,065,603	-$933,843	-$795,974
Total MBS	$2,137,090	$2,656,705	$3,196,634	$3,759,124	$4,347,029
PBS perspective					
Substituted hypotensive medication[a]	-$498,356	-$1,196,223	-$1,789,516	-$2,286,465	-$2,692,994
Commonwealth perspective					
Total cost to Commonwealth	$1,638,734	$1,460,483	$1,407,117	$1,472,659	$1,654,034
Private health funds perspective					
MBGS device	$17,199,770	$17,602,957	$17,999,415	$18,402,789	$18,823,035
Stand-alone hospitalisations	$1,326,711	$2,715,623	$4,165,177	$5,678,027	$7,259,613
Prevented trabeculectomy (CS setting)	-$2,518,413	-$2,291,065	-$2,049,832	-$1,796,374	-$1,531,163
Prevented trabeculectomy (standalone setting)	-$4,264,755	-$8,729,453	-$13,389,090	-$18,252,193	-$23,336,250
Total net cost to private health	$11,743,314	$9,298,062	$6,725,671	$4,032,250	$1,215,235
Whole of health care perspective					
Net cost overall	$13,382,047	$10,758,544	$8,132,788	$5,504,908	$2,869,270

[a] The cost savings per MBGS procedure are based on results from the economic evaluations presented in this and previous submissions. See Section E for more detail.
See budget impact spreadsheet attached (MBGS resubmission_budgetimpact_June2018.xls)

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
The main clinical claim of MBGS versus trabeculectomy is "inferior" to TE in terms of effectiveness but "superior" in terms of safety	There is a lack of properly designed direct comparative studies to demonstrate potential safety and treatment effectiveness of MBGS stent implantation in the standalone setting compared with trabeculectomy. A compromised, naive indirect comparison presented in the SBA did not allow definitive conclusions to be drawn in terms of safety and the treatment effectiveness.
Inappropriate evidence included	Studies of newly diagnosed patients with no prior conservative treatments were incorrectly included in the evidence base. This highlights the importance of further clarification of the MSAC concern about the poorly defined population.
Eligibility criteria	The proposed eligibility criteria are primarily assessed at the clinician's discretion. MSAC may wish to define the appropriate population with more objective restrictions. Further clarification would help to address MSAC's previous major concern on the 'inadequately defined population'.
Comparator	The comparator, clinical algorithm and eligibility should be clarified as the MBGS standalone procedure may also replace further incisional surgery and aqueous tube shunt implantation. Whether MBGS would follow these procedures should also be clarified.
Choice of economic evaluation	Cost analysis is not appropriate; based on the clinical claims, a cost-utility analysis is required.
Financial estimates are uncertain	Financial estimates are based on an estimate of the expected number of MBGS procedures and changes in use of other services (including medication and trabeculectomy or other surgeries), which are uncertain.

ESC discussion

ESC noted that MBGS devices include a variety of implanted, minimally invasive ocular stents and scaffolds that are placed via a corneal incision into the trabecular meshwork (TB MBGS) or suprachoroidal space (SC MBGS) of the eye. The exact positioning of implantation is specific to each device. These devices aim to improve aqueous humour outflow and lower intraocular pressure, which in turn reduces the reliance on topical hypotensive medication.

ESC noted that although MBGS devices differ in design and manufacturer specifications, the complexity and resource burden of the implantation procedure is comparable.
Three TB MBGS devices are available in the Australian market that are relevant to the current application. An SC MBGS device (CyPass Micro-Stent; Alcon) was previously available in Australia but was withdrawn from the global market in August 2018 due to major safety concerns (based on analysis of 5-year post-surgery data). ESC noted that much of the available evidence for effectiveness of MBGS devices is based on the CyPass SC MBGS device.

ESC noted that Glaukos (the manufactures of iStent which is not affected by the withdrawal) has indicated to MSAC that they can provide more information related to iStent and corneal endothelial health and endothelial cell density (the reason for the Cypass withdrawal.). ESC also noted that the applicant is waiting for MSAC advice about whether data for the Cypass SC MBGS device should be removed from the application. ESC noted that the two types of MBGS devices (TB and SC), although similar, work by different mechanisms.

ESC recalled that MSAC previously accepted that the two types of MBGS devices are comparable and should be covered under one MBS item in the cataract surgery setting. ESC noted that, in line with this, the current application for use in the standalone setting includes a single submission-based assessment (SBA) evaluating the evidence and cost-effectiveness for both types of devices.

ESC noted that, although MSAC did not support use of TB and SC MBGS as a standalone procedure in previous Applications 1483 and 1496, the SBA for Application 1541 is largely consistent with documents previously submitted to ESC/MSAC for MBGS as a standalone procedure. ESC noted that the current application should be considered with reference to the original applications, but also noted some key changes from the original applications.

In Section A.1 – PICO Confirmation:

- The resubmission is based on amendments made to the original SBAs for Applications 1483 and 1496 in response to comments by MSAC.
- Documents supporting MBGS as a standalone procedure were submitted to MSAC in April 2018. The MSAC Executive Committee agreed a 'fit for purpose' pathway was appropriate for the new submission and a PICO Confirmation for use of standalone MBGS in Australian clinical practice was not presented to, or ratified by, PASC.

In Section A.2 – Proposed service:

- Additional information has been provided following queries raised during commentaries on the previous applications, but information relating to MBGS standalone stent implantation in this section remains relatively unchanged.

In Section A.3 – Proposal for MBS funding:

- The MBS item descriptor has been revised to more adequately define the patient population who would meet eligibility for the intervention in clinical practice, using the same criteria as used to determine eligibility for current incisional procedures.
- The revised wording is modelled on MBS item 42746 (trabeculectomy), which reflects the intended positioning of MBGS standalone in the OAG treatment pathway.
- ESC noted that the Department has proposed a revised fee of $300.75 for the standalone MBGS implantation procedure (down from $699.45 requested).
- ESC noted that an item descriptor for MBGS stent removal is also proposed but with no requested fee. ESC noted that, in the review of Applications 1483 and 1496, MSAC recommended a fee of $300.75 for stent removal regardless of whether the stent is replaced.

In Section A.4 – Proposed population:

- The proposed population has been redefined in accordance with 2018 ANZGS Guidelines and advice from clinical experts.
- The rationale given for the addition of MBGS as a standalone procedure in the OAG treatment pathway is to provide an alternative treatment option for:
  - patients who are currently being considered for incisional surgical procedures, and
  - patients in whom second-line therapies are indicated but currently available incisional procedures are not possible due to the associated risks.

- ESC noted concerns regarding leakage arising from eligibility criteria being largely assessed at the clinician's discretion. The critique queried whether, given the redefined population are those at a later stage of OAG and precautions listed in the ANZGS Guidelines for managing glaucoma with MBGS, MSAC may consider whether the proposed target population should be restricted to patients with more severe or advanced OAG. ESC noted that the applicant rebutted both these concerns in their pre-ESC response.

- ESC noted further revision to the item descriptor proposed by the Department to define the eligible population with more objective restrictions:

Category 3 – THERAPEUTIC PROCEDURES
MBS item number GLAUCOMA, implantation of, a micro-bypass glaucoma surgery stent system into the trabecular meshwork/suprachoroidal space (irrespective of the number of micro-bypass glaucoma surgery stent systems implanted), in a patient diagnosed with open-angle glaucoma: ~~where conservative therapies have failed, are likely to fail, or are contraindicated~~. a) whose raised intraocular pressure has failed to respond to anti-glaucoma medications or in whom it has been clinically determined that anti-glaucoma medications are either contraindicated or will fail to reduce the patient's intraocular pressure; and b) whose raised intraocular pressure has failed to respond to laser trabeculoplasty or in whom it has been clinically determined that laser trabeculoplasty is either contraindicated or will fail to reduce the patient's intraocular pressure; and c) who would otherwise have been considered for an incisional surgical procedure to manage their open angle glaucoma. Multiple Services Rule (Anaes.) (Assist.) **Fee**: $300.75 **Benefit**: 75% = $225.56

In Section A.5 – Comparator:

- ESC noted that the most appropriate comparator to MBGS is trabeculectomy.
- ESC noted that because MBGS is a second-line option, additional comparators suggested in the PICO of the original applications (e.g. continuation of topical medical therapy, laser trabeculoplasty, the alternative MBGS device) are not considered relevant in this resubmission.
- ESC noted advice in the critique that glaucoma filtering surgery may include aqueous tube shunt implantation in addition to any incisional surgery. The critique suggested that the comparator should be clarified, as the MBGS standalone procedure may also replace further incisional surgery and aqueous tube shunt implantation.

In Section A.7 – Delivery of proposed service:

- ESC noted a discrepancy in the estimated time required for MBGS stent implantation as a standalone procedure. The SBA includes an estimated time of 45–60 minutes (including preparation, stent implantation and post-operative requirements). However, ESC noted that public consultation feedback in the critique for previous Applications 1483 and 1496 indicated that it might take less than 15 minutes of the surgeon's time.

In Section A.8 – Clinical claim:

- ESC noted the clinical claim that MBGS is potentially inferior to trabeculectomy in terms of comparative effectiveness, and superior in terms of comparative safety.

ESC noted that, according to the clinical algorithm provided, patients can undergo an MBGS standalone procedure following trabeculectomy or further incisional surgery/aqueous tube shunt implantation. The appropriateness of, and the evidence base for these treatment pathways, needs further clarification. ESC noted that clarification is also required as to how many MBGS procedures may be performed per eye.ESC noted no issues with the revised PICO provided in the SBA for the current application.

ESC noted that the systematic review of published and unpublished literature has not been updated in the new application, and that the critique had concerns about the process of study selection in the systematic review because literature annotation was done by only one reviewer. ESC noted that the three-stage approach for evidence appraisal requested in MSAC guidelines was poorly performed, and a GRADE evidence profile was not provided in the SBA. ESC noted that, overall, the literature review and evidence appraisal are incomplete.

ESC noted that the evidence base comprised only two RCTs (three publications) and 11 non-randomised studies for MBGS standalone, and the two UK National Trabeculectomy Surveys for trabeculectomy. ESC noted that the critique recommended that RCTs in treatment naive patients (Vold 2016 for MBGS, and Burr 2012 systematic review that included the Collaborative Initial Glaucoma Treatment Study [CIGTS] for trabeculectomy) be excluded.

ESC noted that the quality of evidence provided in the SBA is poor for a number of reasons:

- There are no direct RCTs comparing MBGS stent implantation and trabeculectomy in OAG patients. The vast majority of evidence is from non-randomised studies.
- Studies in treatment-naive patients were included, so the applicability of results to the proposed population (MBGS as second-line treatment in patients with uncontrolled intraocular pressure following prior conservative treatments) is uncertain. Heterogeneity in study design limited any definitive conclusions about reduction in topical medications.
- Safety outcomes were poorly reported in RCTs of MBGS stent implantation, which restricts the direct comparison of MBGS with topical medications. Safety outcomes reported in non-randomised cohort studies were considered low-level evidence.
- The UK National Trabeculectomy Survey included as the key evidence for safety of trabeculectomy was conducted in 1996. ESC agreed with the critique that a more recent UK survey with a minimum follow-up of 2 years (Kirwan 2013) should be included, as it more accurately captures the reduced complications and improved outcomes of trabeculectomy over time.
- Given the lack of a common reference arm in datasets for MBGS and trabeculectomy, a formal indirect comparison was not possible. The SBA therefore presented an informal, naive indirect comparison, which was compromised by heterogeneous populations and study designs, limited exchangeability, different follow-up times and out-of-date evidence. This meant that the claimed superiority in safety (incidence of surgical complications and other adverse effects) of MBGS compared with trabeculectomy is highly uncertain, and the claimed superiority in effectiveness (control of intraocular pressure) of trabeculectomy compared with MBGS is uncertain.

ESC noted that, in terms of safety, data from the SBA indicate that MBGS stent implantation demonstrates a different profile of potential adverse events to trabeculectomy, which is consistent with the less invasive nature of MBGS. The two RCTs of MBGS reported surgical

complications in 3.2% and 3.7% of procedures. For trabeculectomy, the CIGTS RCT reported event rates for a number of single adverse events of over 10%. The UK National Trabeculectomy Survey for 1996 reported adverse event rates of 20%; however, the more recent survey (Kirwan 2013) showed a substantial reduction in adverse events due to improved intraoperative techniques and professionally trained specialists.

ESC noted that in terms of effectiveness, data from the SBA indicate that the standalone MBGS procedure was associated with reduced intraocular pressure and reduced need for ocular hypotensive therapy. The reduction in intraocular pressure was maintained until 5 years after implantation, and the majority of patients maintained intraocular pressure without additional hypotensive medication. ESC noted that outcomes reported in the Burr 2012 systematic review showed trabeculectomy to be associated with a significantly greater mean change in intraocular pressure from baseline compared with medical therapy.

ESC noted the suggestion in the critique that a non-randomised, prospective, comparative cohort study of MBGS versus trabeculectomy in OAG patients (Pahlitzsch 2017) may provide valid comparative outcomes for the purpose of an informal indirect comparison. This study demonstrated trabeculectomy to give superior control of intraocular pressure in the early stage following surgery ($p = 0.046$) and consistently significantly lower glaucoma medications up to 6 months post-operatively ($p < 0.001$).

ESC noted that, although the study was prone to bias due to the non-randomised design, the clinical claim of superior effectiveness associated with trabeculectomy appears appropriate. ESC noted that a number of current trials may provide more data in future, though not in the short term.

ESC noted that, given the proposed service is likely to be a day procedure, the most appropriate categorisation for standalone MBGS in the Private Health Insurance (Benefit Requirement) Rules is Type B (Non Band Specific).

ESC noted the following clinical policy issues for MSAC:

- The population who would be eligible for the service is still inadequately defined.
- Unlike the current listing for glaucoma filtering surgery, no separate MBS item number is proposed for repeated MBGS implantation. The frequency of repeated MBGS implantation per eye has not been specified.
- Issues remain with wording of the item descriptor
  - the stated concept of ‘likely to fail’ is of concern; without an objective threshold by which a treatment failure could be predicted, the criterion is open to broad interpretation and misuse
  - similarly, ‘conservative therapies’ could be more prescriptive to explicitly encompass topical medication, oral medication and laser trabeculoplasty, which would be considered prior to MBGS as outlined in the assessment report (p. 28)
- Explicit direction of whether or not the item applies per eye is required.
- ESC noted that the economic evaluation presented is a cost analysis, which is inappropriate for the clinical claim of inferior effectiveness and superior safety. The choice and quantification of outcomes were not documented or justified which, taken with the poor quality of the evidence, makes assumptions within and conclusions from the cost analysis highly uncertain... ESC considered that a cost-utility analysis is required to evaluate net benefits.
- ESC noted that the cost analysis included two pathways for MBGS, assuming that all non-responders to MBGS would receive a trabeculectomy. ESC noted that the cost

analysis assumed a success rate for MBGS of 83%; the remaining 17% were assumed to receive subsequent trabeculectomy. The success rate of trabeculectomy was assumed to be 100% regardless of the pathway (with or without prior MBGS). However, ESC noted issues with the definition of 'success': different studies use different measures of success, and the success rate of interventions is very dependent on the definition of success, the timepoint at which success is calculated and the population.

ESC noted that the cost analysis assumed quality of life benefits of avoiding adverse events were the same regardless of the pathway, but this was not quantified. ESC noted statements in the applicant's pre-ESC response that 'quantification of incremental life years and QALYs accrued as a result of the interventions is not necessary', with inadequate justification. .

ESC noted that key inputs to the cost analysis were costs of the respective procedures, incidence and costs of associated adverse events, and the proportion of MBGS patients requiring subsequent trabeculectomy.

ESC noted that the cost analysis found the total cost per patient for MBGS to be less than for trabeculectomy (due to cost offsets from reduced costs of the intervention and managing adverse events). However, ESC noted that the difference was very small ($87) which highlights the importance of uncertainty around the key inputs.

ESC noted that the cost input for trabeculectomy included 12 post-operative follow-up consultations. ESC considered this to be excessive; most studies of trabeculectomy include around nine post-operative consultations. ESC also noted that the input cost of the MBGS device ($1440) is an average of the prices of the different devices available.

ESC noted that costs related to adverse events associated with trabeculectomy were derived from the 1996 UK National Trabeculectomy Survey and the Burr 2012 systematic review (that included OAG patients with no prior treatments). However, ESC noted that using adverse events data from the more recent UK survey (Kirwan 2013) reduced the cost saving of MBGS compared to trabeculectomy from $87 to $31.58.

ESC noted that the estimate of the proportion of patients who would require trabeculectomy due to MBGS failure (17.1%) was derived from the DUETTE study (an open-label, single-arm study of uncertain quality). Costs of subsequent trabeculectomy were calculated by applying this percentage to the costs of the trabeculectomy procedure and of associated adverse events.

ESC noted that the cost analysis was highly sensitive to small changes in key inputs. ESC noted the following threshold analysis (no cost saving):

- using Kirwan (2013) adverse events data and an MBGS failure rate of 18
- using the cost of one of the available MBGS devices (iStent, $1536) instead of an average price;
- using nine follow-up consultations for trabeculectomy instead of 12 (Rodriguez-Una et al. 2016)

ESC noted that use of concurrent medications with interventions has not been included in the evaluation. ESC noted that this may push the potential impact on healthcare costs and quality of life in favour of MBGS. ESC noted the study by Pahlitzsch et al. (2017) (a prospective observational study) that showed a significant decrease in the number of glaucoma medications at all post-operative timepoints in favour of trabeculectomy (versus MBGS). ESC noted the applicant's pre-ESC response that 'due to a lack of randomised comparative

data, there is uncertainty as to whether any differences would be observed in the capacity to reduce the need for ocular hypotensive therapy between MBGS and trabeculectomy post-intervention'.

ESC noted that the net cost to the MBS was estimated to be $2.1 million in year 1, rising to $4.3 million in year 5. However, ESC noted that the financial and budgetary impacts are uncertain due to:

- uncertainty about the estimated number of MBGS procedures per year
  - the estimate of between 12,000 (year 1) and 13,000 (year 5) includes both standalone and combined settings; in calculating costs, it was assumed that standalone MBGS would constitute 10% of the total in year 1, rising to 50% in year 5 which is uncertain
  - the estimate included only privately insured patients; there is uncertainty about the number of patients who may receive MBGS in the public hospital setting and the resultant impact on government budgets
- uncertainty about the effect of a change in cost of other services, for example
  - reductions in medication use and trabeculectomy
  - cost-saving associated with avoidance of laser trabeculoplasty should not be included because they are not relevant to the target population
- the exclusion of costs for subsequent trabeculectomy after MBGS failure.

ESC also noted that the lower proposed fee in revised item descriptors will have an impact on the economic evaluation.

ESC noted the following key economic issues for MSAC:

- Cost analysis is not appropriate.
- Results of the economic evaluation are highly uncertain due to the poor quality of evidence and analysis, the inclusion of inappropriate evidence, and the high level of uncertainty in key inputs.
- Financial estimates are uncertain due to uncertainty about the expected number of MBGS procedures and the potential changes in use of other services.

ESC also noted a health technology assessment commissioned by the Canadian Agency for Drugs and Technologies in Health (CADTH), looking at the optimal use of minimally invasive glaucoma surgery. ESC suggested that it would be useful for MSAC to refer to the 12 research questions outlined in the project proposal to inform their deliberations.

15. Other significant factors

Nil

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

The applicant is disappointed with MSAC's decision not to recommend the micro-bypass glaucoma surgery (MBGS) device implantation as a standalone procedure in patients with open angle glaucoma for inclusion on the MBS. The applicant is concerned MSAC's reasoning the effectiveness of MBGS is uncertain is inconsistent with the previous recommendation to include MBGS on the MBS in patients undergoing cataract surgery and are concerned this inconsistency will potentially confuse patients and contribute to inequitable access. The applicant are disappointed MSAC considered the eligibility criteria to be poorly defined because we based it on the criteria developed by MSAC for the more invasive and costly trabeculectomy procedure. The applicant believes the cost-analysis provides a good basis for MSAC decision making because it appropriately incorporates the

costs of the potentially inferior effectiveness of MBGS relative to trabeculectomy. The applicant looks forward to better understanding MSAC's position on these issues and will continue to work with the department and with MSAC to ensure equitable access to MBGS in the future.

Glaucoma Australia disagree with the MSAC decision which now limits access to the new glaucoma drainage stents, a valuable tool to lower eye pressure, for those who do not need cataract surgery, or already have had cataract surgery. Please see the Glaucoma Australia website for more information (www.glaucoma.org.au).

17. Further information on MSAC

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