



Australian Government

Department of Health

Application 1483:

Trabecular bypass micro-invasive glaucoma surgery (MIGS) device implantation in patients with mild-to-moderate primary open-angle glaucoma

PICO Confirmation

(to guide a new application to MSAC)

(Version 0.1)

This PICO Confirmation Template is to be completed to guide a new request for public funding for new or amended medical service(s) (including, but not limited to the Medicare Benefits Schedule (MBS)). It is relevant to proposals for both therapeutic and investigative medical services.

Please complete all questions that are applicable to the proposed service, providing relevant information only.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment (HTA Team) on the contact number and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Version Control

Document History

Version Number	Date Changed	Author	Reason for Change
0.1	10 March 2016	Bianca Ledbrook	Final template for publication
1.0	3 April 2017	Adelaide Health Technology Assessment	Draft PICO Confirmation for discussion at PASC
2.0	19 May 2017	Adelaide Health Technology Assessment	Edits to PICO Confirmation, based on ratified PASC outcomes

Document Approval

Version Number	Date Changed	Author	Reason for Change
0.1	2016		Template released for publication
2.0	1 June 2017		PICO Confirmation ratified by PASC Chair

Summary of PICO criteria to define the questions to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Population 1

Component	Description
Patients	Patients with primary open-angle glaucoma (POAG) who have a current cataract co-morbidity and are receiving topical hypotensive drugs to lower intraocular pressure (IOP)
Intervention	Cataract surgery with concurrent trabecular bypass micro-invasive glaucoma surgery (MIGS) stent implantation with/without additional medication
Comparators	Cataract surgery plus medical management with topical hypotensive drugs Cataract surgery with concurrent suprachoroidal MIGS stent implantation with/without additional medication Cataract surgery with concurrent trabecular bypass MIGS using different stents with/without additional medication
Outcomes	<p>Clinical Effectiveness: Rate of vision impairment/loss, proportion of vision impairment/loss, time to vision impairment/loss, mean IOP reduction from baseline, proportion of patients with IOP reduction $\geq 20\%$, proportion of patients with IOP ≤ 18 mmHg, time to increase in IOP, change in the number of ocular hypotensive medications, proportion of patients on medication quality of life (effect on daily living activities, e.g. driving, walking, and reading), health-related quality of life (psychological burden due to fear of blindness, social withdrawal, and depression).</p> <p>Safety: Intraoperative complications, post-operative ocular complications, secondary surgical interventions, corrected distance visual acuity, visual field mean deviation</p> <p>Cost-effectiveness: Cost, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio</p> <p>Australian Government healthcare costs</p>
Research questions	<ol style="list-style-type: none"> 1. What is the safety, effectiveness, and cost-effectiveness of cataract surgery with concurrent trabecular bypass MIGS stent implantation with/without additional medication compared with cataract surgery plus medical management with topical hypotensive drugs in patients with POAG who have a cataract co-morbidity? 2. What is the safety, effectiveness, and cost-effectiveness of trabecular bypass MIGS stent implantation compared with suprachoroidal MIGS stent implantation in patients with POAG who are undergoing concurrent cataract surgery for a cataract co-morbidity? 3. What is the comparative safety, effectiveness, and cost-effectiveness of different trabecular bypass MIGS stents in patients with POAG who are undergoing concurrent cataract surgery for a cataract co-morbidity?

The PICO criteria for populations 2 and 3, as amended by PASC (based on applicant comments), are shown in the next two tables. If the applicant considers that populations 2 and 3 should be combined, the submission will need to be explicit regarding whether laser trabeculoplasty becomes a prior-intervention, or a comparator.

Population 2

Component	Description
Patients	Patients with primary open-angle glaucoma (POAG) who have previously undergone cataract surgery and in whom medical management with topical hypotensive drugs alone is either no longer effective or not tolerated
Intervention	Trabecular bypass micro-invasive glaucoma surgery (MIGS) stent implantation
Comparator	Laser trabeculoplasty Suprachoroidal MIGS stent implantation Different trabecular bypass MIGS stents
Outcomes	<p>Clinical Effectiveness: Rate of vision impairment/loss, proportion of vision impairment/loss, time to vision impairment/loss, mean IOP reduction from baseline, proportion of patients with IOP reduction $\geq 20\%$, proportion of patients with IOP ≤ 18 mmHg, time to increase in IOP, change in the number of ocular hypotensive medications, proportion of patients on medication quality of life (effect on daily living activities, e.g. driving, walking, and reading), health-related quality of life (psychological burden due to fear of blindness, social withdrawal, and depression)</p> <p>Safety: Intraoperative complications, post-operative ocular complications, secondary surgical interventions, corrected distance visual acuity, visual field mean deviation</p> <p>Cost-effectiveness: Cost, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio</p> <p>Australian Government healthcare costs</p>
Research questions	<ol style="list-style-type: none"> 4. What is the safety, effectiveness, and cost-effectiveness of trabecular bypass MIGS stent implantation compared with laser trabeculoplasty in patients with POAG who have previously undergone cataract surgery? 5. What is the safety, effectiveness, and cost-effectiveness of trabecular bypass MIGS stent implantation compared with suprachoroidal MIGS stent implantation in patients with POAG who have previously undergone cataract surgery? 6. What is the comparative safety, effectiveness, and cost-effectiveness of different trabecular bypass MIGS stents in patients with POAG who have previously undergone cataract surgery?

Population 3

Component	Description
Patients	Patients with primary open-angle glaucoma (POAG) who have no history of cataracts and in whom laser trabeculoplasty has either failed or is unlikely to be successful
Intervention	Trabecular bypass micro-invasive glaucoma surgery (MIGS) stent implantation
Comparator	Trabeculectomy Other incisional surgical procedures Suprachoroidal MIGS stent implantation Different trabecular bypass MIGS stents
Outcomes	<p>Clinical Effectiveness: Rate of vision impairment/loss, proportion of vision impairment/loss, time to vision impairment/loss, mean IOP reduction from baseline, proportion of patients with IOP reduction $\geq 20\%$, proportion of patients with IOP ≤ 18 mmHg, time to increase in IOP, change in the number of ocular hypotensive medications, proportion of patients on medication quality of life (effect on daily living activities, e.g. driving, walking, and reading), health-related quality of life (psychological burden due to fear of blindness, social withdrawal, and depression)</p> <p>Safety: Intraoperative complications, post-operative ocular complications, secondary surgical interventions, corrected distance visual acuity, visual field mean deviation</p> <p>Cost-effectiveness: Cost, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio</p> <p>Australian Government healthcare costs</p>
Research questions	<p>7. What is the safety, effectiveness, and cost-effectiveness of trabecular bypass MIGS stent implantation compared trabeculectomy or other incisional surgical procedures in patients with POAG who have no history of cataracts?</p> <p>8. What is the safety, effectiveness, and cost-effectiveness of trabecular bypass MIGS stent implantation compared suprachoroidal MIGS stent implantation in patients with POAG who have no history of cataracts?</p> <p>9. What is the comparative safety, effectiveness, and cost-effectiveness of different trabecular bypass MIGS stents in patients with POAG who have no history of cataracts?</p>

Population

Glaucoma is a chronic, degenerative optic neuropathy characterised by progressive vision loss due to the loss of retinal ganglion cells and optic nerve damage (Kwon et al. 2009; Quigley 2011). It is the number one cause of irreversible vision loss and the second leading cause of blindness worldwide (Conlon, Saheb & Ahmed 2017). Peters et al. (2013) reported that the risk of blindness in at least 1 eye and bilateral blindness from glaucoma were 26.5% and 5.5%, respectively, after 10 years, and 38.1% and 13.5% at 20 years.

An increase in intraocular pressure (IOP) is thought to be a major cause of glaucoma. IOP increases either when too much aqueous humour fluid is produced or when aqueous humour outflow is decreased. There are two outflow pathways, for a diagram of the structure of the eye showing these pathways, see footnote below¹. In the trabecular pathway, the trabecular meshwork is responsible for draining the aqueous humour from the anterior chamber. It is a spongy tissue located around the base of the cornea, between Schlemm's canal and the anterior chamber. The trabecular meshwork drains the aqueous humour into Schlemm's canal, which is a circular lymphatic-like vessel that delivers the collected aqueous humour into the episcleral blood vessels. The uveo-scleral pathway starts with the aqueous humour filtering between the muscle bundles of the ciliary body; with this being the rate-limiting step. The aqueous humour flows into the suprachoroidal space, through the sclera and into the lymphatics to be drained away from the eye.

Glaucoma is referred to as open-angle or closed-angle depending on whether the drainage channels for aqueous humour in the front of the eye appear open or closed (Boland et al. 2013). In primary open angle glaucoma (POAG), the decreased outflow is attributed to increased resistance due to age-related thickening or sclerosis of the trabecular meshwork and absence of giant cells in Schlemm's canal. POAG is the most common form and is triggered by both environmental and genetic risk factors; up to 50% of patients have a positive family history of POAG (Allingham, Liu & Rhee 2009; Janssen et al. 2013).

A diagnosis of POAG is made only after the other types of glaucoma have been excluded and is based on a characteristic progressive enlargement of the optic cup (disc cupping) (Foster et al. 2002; Leske 1983). The vertical cup:disc ratio is a simple, relatively robust index of glaucomatous loss of the neuroretinal rim. Vision field defects may not yet be detected in mild disease, but as the disease progresses visual field abnormalities become more apparent. High IOP >21 mmHg, is a major risk factor for both developing POAG and for progression to irreversible vision loss, however, 15–40% of patients with POAG have normal IOP (Maier et al. 2005).

¹ In SlideShare, *Pharmacotherapy of glaucoma, Aqueous humour dynamics*. Slide 7 shows the structure of the eye with the two aqueous humour outflow pathways and is available from URL: <<https://www.slideshare.net/manjuprasad16/pharm-of-glaucoma>> accessed 23 March 2017

Patients with confirmed POAG expected to access trabecular bypass micro-invasive glaucoma surgery (MIGS) stent implantation through the Medicare Benefits Schedule (MBS) can be broadly divided into two groups:

- Patients who will undergo implantation in conjunction with cataract surgery (population 1). MIGS stent implantation would be considered earlier in the management pathway for these patients (depending on the need for cataract surgery), and would be an adjunct to topical hypotensive medication;
- Patients who will receive the intervention as a stand-alone procedure. These patients can be further divided in two sub-groups:
 - patients who have previously undergone cataract surgery (referred to as pseudophakic) and who are currently unable to maintain target IOP with maximally tolerated topical hypotensive medication (population 2); and
 - patients who do not exhibit any signs of cataract development (referred to as phakic) in whom conventional medication management and less invasive interventional techniques (i.e. laser trabeculoplasty) have not been successful (population 3).

As patients from populations 2 and 3 comprise less than 5% of all patients having a MIGS implantation procedure, the applicant proposed that populations 2 and 3 be combined and defined as:

- Patients who will receive the intervention as a stand-alone procedure (population 2). In clinical practice, MIGS will be positioned where conservative therapies have failed, are likely to have failed, or are contraindicated. In this population MIGS stent implantation would supplant or delay other incisional surgeries, such as trabeculectomy (population 2).

The PICO Advisory Sub-Committee (PASC) considered this was a reasonable approach (i.e. an assessment in which populations 2 and 3 have been combined), given the paucity of evidence for these patients. The submission will need to define 'conservative therapies', to be explicit regarding whether this includes laser trabeculoplasty or not. If it does, then the implication of combining the populations will be that MIGS stent implantation for population 2 will be later in the pathway (after laser trabeculoplasty, rather than an alternate to laser trabeculoplasty). If 'conservative therapies' excludes laser trabeculoplasty, then population 3 will be expanded to allow earlier treatment (i.e. laser trabeculoplasty becomes a comparator, rather than required prior-treatment).

Prevalence of POAG and cataracts among adults in Australia

Glaucoma affects approximately 66.8 million people worldwide, and up to 50% of people in the industrialised world are unaware of their condition and are therefore not receiving appropriate treatment (Conlon, Saheb & Ahmed 2017). In 2004, it was estimated that between 2.7% and 3.7% of Australians aged 55 years or more had glaucoma². There was no significant difference in prevalence rates between men and women.

Although glaucoma and cataracts are not related conditions, co-morbidity will occur in many patients. This is likely due to the large number of older people with cataracts. Approximately 31% of

² Based on Australian Bureau of Statistics and National Health survey data, Table A4 in *Vision problems among older Australians*. Available from <<http://www.aihw.gov.au/publication-detail/?id=6442467733>> (accessed 7 March 2017)

Australians aged 55 or more suffer from cataracts³. Age-specific rates for cataracts are well over 70% for both men and women aged 80 or more.

Rationale

There are five randomised controlled trials (RCTs) investigating the effectiveness of combined trabecular bypass MIGS and cataract surgery listed in the summary of evidence. Patients enrolled in these trials all had a diagnosis of POAG with mild to moderate disease (cup:disc ratio of ≤ 0.8) and an elevated IOP (un-medicated IOP >18 and ≤ 36 mmHg). Thus, the population in the evidence base matches population 1.

There are also three RCTs investigating the effectiveness of trabecular bypass MIGS as a stand-alone procedure. All three trials excluded patients with cataracts and one (Vold et al. 2016) also excluded patients with prior cataract surgery. In the other two trials only 2% (Katz et al. 2015) and 3% (Fea et al. 2014) of patients had had previous cataract surgery. Patients in these trials most closely match population 3, which suggests there may be little evidence to support the use of trabecular bypass MIGS in population 2.

The phakic patients enrolled in 2 of the studies were using either one (Fea et al. 2014) or two (Katz et al. 2015) medications and required additional IOP lowering to control their OAG. In the study by Vold et al (2016) the patients were newly diagnosed with POAG and had not undergone any treatment. Although there is evidence for phakic patients who have mild to moderate disease (cup:disc ratio of ≤ 0.9), they have milder IOP control problems than the population specified in the application. These patients did not receive previous invasive interventional techniques, such as laser trabeculoplasty, and therefore would not be eligible for trabecular bypass MIGS, based on the clinical pathway provided by the applicant for population 3.

Intervention

Trabecular bypass MIGS stent implantation procedures involve a minimally invasive micro-incision approach (usually into the cornea), to minimize tissue scarring, and allow for the possibility of other glaucoma procedures such as trabeculectomy or aqueous/tube stent implantation to be performed in the future if needed (Gonnermann et al. 2017).

The proposed service involves the delivery of a trabecular bypass stent – pre-loaded on an inserter specific to each device – into the trabecular meshwork of the eye. The implantation of the stent(s) ab interno (from inside the eye), via a corneal incision, is guided by gonioscopy. The exact positioning within the anterior structures (trabecular meshwork and Schlemm’s canal) are specific to each device. However, the complexity and resource intensity of the implantation procedure is comparable regardless of trabecular bypass stent implanted (iStent or Hydrus). The applicant has indicated that the procedure requires approximately 30-60 minutes of operating and preparation time as a stand-alone procedure. A response to the targeted consultation survey on MSAC application 1483 indicated it would take approximately 15 minutes of a surgeon’s time and significantly less than 15 minutes if combined with cataract surgery. The applicant advised that fifteen minutes is considered the minimum amount of professional time required when the stent implantation procedure is performed in conjunction with cataract surgery, and overall procedural time for an experienced surgeon does not significantly differ between devices. PASC considered that,

³ AIHW website. Available from <<http://www.aihw.gov.au/media-release-detail/?id=6442464587>> (accessed 7 March 2017)

if the length of time did not vary for cataract removal (with or without MIGS), further justification of the MBS fee will need to be provided during the assessment phase.

PASC noted that goniotomy is traditionally performed in a paediatric patient population for congenital glaucoma, and this application expands that population to an older patient group.

Three stent devices are relevant to trabecular bypass MIGS in the treatment of patients with mild-to-moderate POAG, with or without cataracts: the iStent, the iStent inject system, and the Hydrus Microstent.

The iStent Trabecular Micro-Bypass Stent is an L-shaped heparin-coated titanium device, 0.33 mm in height and 1.00 mm in length, with a snorkel length of 0.25 mm (Neuhann 2015). The iStent is preloaded into a disposable inserter to enable accurate insertion of the device into the Schlemm's canal (Neuhann 2015). The surgeon positions the iStent inserter through a corneal incision using gonioscopy to guide the stent through the trabecular meshwork and into Schlemm's canal in the nasal portion of the aqueous drainage system. Once implanted, the stent body is in the Schlemm's canal with the snorkel protruding into in the anterior chamber (Gallardo et al. 2016). This creates a conduit for aqueous humour drainage from the anterior chamber into Schlemm's canal.

The iStent inject system is a second-generation heparin-coated titanium device, which provides the ability to house two stents in the trabecular meshwork to increase outflow while entering the eye only once. Under gonioscopic view, the injector is positioned such that two iStents are implanted through the trabecular meshwork into the nasal Schlemm's canal, separated by approximately sixty degrees (Gonnermann et al. 2017; Lindstrom et al. 2016).

PASC considered that clarification is needed on use of two stents (rather than one) in clinical practice, as this will have Prostheses List benefit implications (especially given the iStent inject system is more expensive than the single iStent device, and inclusion of the criteria that define the circumstances under which the more expensive stent would be used).

The applicant advised that use of two stents produces superior outcomes to the single stent procedure (i.e. one iStent results in a 6 mm Hg reduction in IOP, while two stents (iStent inject) results in a 14–16 mmHg reduction). The applicant advised that, for every 1 mmHg reduction, there is a 10% reduction in disease progression.

Both the iStent Trabecular Micro-Bypass Stent and the iStent inject system have Therapeutic Goods Administration (TGA) approval for use in conjunction with cataract surgery in subjects with mild to moderate OAG currently treated with ocular hypotensive medication. The sponsors are currently seeking an amendment for implantation with or without concomitant cataract surgery. The estimated date for the TGA decision is between May and July, this year.

The Hydrus Microstent is the longest of the MIGS stent devices (8 mm long implant), and serves as an intra-canalicular scaffold once implanted into Schlemm's canal. The delivery device makes a small incision through the trabecular meshwork and the inner wall of Schlemm's canal. The microstent is then advanced along the canal, with 1-2mm of stent remaining in the anterior chamber. The stent mechanically dilates and holds open Schlemm's canal. The length of the Hydrus Microstent is thought to open approximately one quarter of Schlemm's canal, enabling the aqueous humour to flow into open downstream collector channels. The Hydrus Microstent has TGA approval for use in patients with POAG as a standalone treatment or in conjunction with cataract surgery.

Trabecular bypass MIGS stent implantation has been performed in Australia for the last 2–3 years and has been funded under MBS item number 42758 (goniotomy). However, a Medicare Benefits Schedule (MBS) review has determined that item 42758 does not cover the implantation of trabecular bypass MIGS stents and an amendment explicitly excluding this procedure will be added to this item number, effective 1 May 2017.

The applicant confirmed that trabecular bypass MIGS stent implantation is likely to be performed only once per eye (maximum of two procedures per person). However, the patient may need repositioning or removal of the stent at a later date.

The applicant also stated there are limitations with the procedure, being that it is ineffective for complete obstruction of trabecular meshwork.

Rationale

MIGS stent implantation in patients with POAG is intended to reduce the medication burden for patients while maintaining IOP at a target level. This may be achieved by either directly reducing the number of hypotensive medications required per day (on average one less medication is required), or avoiding the need for an increase in medication over time. Following insertion of a stent, 80% of patients no longer need topical medication.

Cataract surgery is common among patients with POAG, especially those aged 55 years or older. Thus, MIGS stent implantation will take place at the same time as the cataract surgery in approximately 20% of patients with cataracts (population 1), because addressing these two conditions in a single operation minimises the risk of surgery-related complications (i.e. infection). In pseudophakic patients who have had previous cataract surgery and in whom medical management with topical hypotensive drugs alone is either no longer effective or not tolerated (population 2) MIGS stent implantation would occur as a stand-alone procedure instead of laser trabeculoplasty. In these patients there is no likelihood of damaging the lens, thus MIGS can occur earlier in the progression of glaucoma than in phakic patients with no history of cataracts who still have their natural lens (population 3). In patients with a natural lens there is less space in the eye, and there is a risk of damaging the lens; therefore, MIGS stent implantation is delayed until laser trabeculoplasty has failed (or is unlikely to be successful) and is performed instead of a trabeculectomy.

The potential for MIGS to be performed prophylactically in patients requiring cataract surgery should be addressed in the assessment.

Comparators

There are three different types of comparators to trabecular bypass MIGS stent implantation: the comparators that would be considered in the absence of MIGS stent implantation, a comparison with an alternative form of MIGS stent implantation using a suprachoroidal micro-stent, and a comparison between the three different trabecular bypass MIGS stents.

Suprachoroidal MIGS stent implantation

The CyPass suprachoroidal micro-stent is a polyimide tube with a fenestrated lumen. It is 6.35 mm long with an inner diameter of 0.30 mm and the outer diameter of 0.43 mm. The implantation of the stent ab interno, via a corneal incision, is guided by gonioscopy and placed in the angle of the eye,

with the proximal end extending into the anterior chamber to allow outflow of aqueous fluid in the supraciliary and suprachoroidal space, where the distal end resides, via the uveoscleral pathway.

Population 1: Patients with POAG and a current cataract co-morbidity

In patients who require cataract surgery, MIGS stent implantation would be considered early in the management algorithm, as an adjunctive treatment to topical hypotensive medication. The cataract and MIGS stent implantation would be performed together as one procedure. These patients would not yet be considered for laser trabeculoplasty in the current clinical algorithm. Thus, the only appropriate comparator to MIGS stent implantation for POAG patients with a cataract co-morbidity is cataract surgery with medical management of IOP with ocular hypotensive drugs.

Topical hypotensive medication represents the first-line therapy for patients with POAG. Patients start with a single topical medication, and increase the dosing frequency and number of therapies, as required, in order to maintain a target IOP. There are four main classes of pharmacotherapy available through the Pharmaceutical Benefits Scheme (PBS) that are used to treat glaucoma in Australia:

- Prostaglandin analogues are the first choice for most newly diagnosed patients and are the most commonly prescribed hypotensive medications for glaucoma:
 - Currently available on the PBS: bimatoprost, latanoprost, tafluprost and travoprost;
- Beta-blockers are the second most commonly prescribed class of topical glaucoma medications and are also used as first-line therapy for some patients:
 - Currently available on the PBS: betaxolol and timolol;
- Alpha agonists and carbonic anhydrase inhibitors are commonly used as adjunctive therapy when IOP is inadequately controlled with one medication;
 - Currently available on the PBS: brimonidine, apraclonidine, brinzolamide, dorzolamide;
- Fixed combination agents of the above classes are also available:
 - Currently available on the PBS:
 - Prostaglandin analogues bimatoprost, latanoprost and travoprost in combination with beta-blocker timolol;
 - Alpha agonists and carbonic anhydrase inhibitors brimonidine, brinzolamide and dorzolamide in combination with beta-blocker timolol;
 - Alpha agonist (brimonidine) in combination with a carbonic anhydrase (brinzolamide).

Population 2: Patients with POAG who have previously undergone cataract surgery

Under the proposed clinical pathway, patients who have had previous cataract surgery and are experiencing inadequate IOP control with maximal-tolerated hypotensive medication or due to poor compliance, or other treatment-related adverse events would be considered for MIGS stent implantation instead of laser trabeculoplasty. This is because these patients are not at risk of damage to the lens from MIGS. As the alternative treatment for these patients would be laser trabeculoplasty, this would be the correct comparator to MIGS stent implantation for these patients. Laser trabeculoplasty is reimbursed under MBS item numbers 42782 (up to 4 treatments in 2-year period) and 42783 (5th or subsequent treatment in 2-year period).

There are two main types of laser trabeculoplasty. Argon laser trabeculoplasty uses a laser to initiate cellular and biochemical changes to the junction of the anterior pigmented and posterior non-pigmented trabecular meshwork, with the power titrated to achieve blanching (Sihota 2011). These changes result in increased aqueous humour flow and lower IOP. However, selective laser trabeculoplasty is now more commonly performed in many countries including Australia as the thermally mediated radiation damage caused by the argon laser is confined to the pigmented trabecular meshwork cells, which absorb more of the applied laser energy than the surrounding cells (Realini 2008). The two laser trabeculoplasty methods are compared in Table 1. According to the National Health and Medical Research Council (NHMRC) *Guidelines for the Screening, Prognosis, Diagnosis, Management and Prevention of Glaucoma 2010* (NHMRC 2010), the literature reports that argon laser trabeculoplasty and selective laser trabeculoplasty are equally effective in reducing IOP.

Table 1 Comparison of argon laser trabeculoplasty and selective laser trabeculoplasty surgeries

	Argon laser trabeculoplasty	Selective laser trabeculoplasty
Spot size	50 µm	400 µm
No. of spots	50 spots equally spaced over 180° of the TM	50 spots covering a total of 360° of the TM
Energy used	500 mW	<1% of ALT
Fluence	40,000 mJ/mm ²	>0.00015% of ALT
Exposure time	0.1 second	3 nanoseconds
Effect	Thermal damage	No thermal damage

Source: Sihota (2011)

The NHMRC guidelines recommend laser trabeculoplasty for older patients with glaucoma who are at risk of visual loss within their lifetime, particularly when the following factors apply:

- there is difficulty with administering eye drops;
- patients are unresponsive to medication alone; or,
- patients are poor candidates for incisional surgery.

The patients in population 2 fall within these parameters.

Population 3: Patients with POAG who have no history of cataracts

Currently, patients with no history of cataracts in whom the target IOP is not being achieved and laser trabeculoplasty has failed or is not likely to succeed would be considered for incisional surgical approaches, such as trabeculectomy. MIGS stent implantation is being proposed as an alternative procedure at this stage, trabeculectomy as well as other incisional surgical approaches would be the appropriate comparators to MIGS stent implantation in this population. Incisional filtration surgery, including trabeculectomy, is reimbursed under MBS item numbers 42746 (first surgery) and 42749 (subsequent surgeries).

The purpose of surgical treatment for POAG is to prevent glaucoma-induced visual disability. Incisional surgery is often considered a third choice approach after medication and laser therapy due to the risk of damaging the natural lens. Incisional surgical procedures include:

Trabeculectomy:

Incisional filtering microsurgery that involves surgically creating a drainage channel between the anterior chamber and subconjunctival space. The subconjunctival space consists of loose connective tissue and the surgical dissection and subsequent aqueous flow are believed to stimulate fibrosis in this tissue which reduces the outflow of aqueous over time.

If populations 2 and 3 are combined, the applicant has indicated trabeculectomy would be the appropriate comparator for the merged population. The submission-based assessment should be explicit regarding whether laser trabeculoplasty is a prior-treatment, or a possible comparator.

Filtrating surgeries, such as deep sclerectomy, viscocanalostomy and canaloplasty:

These surgeries are not widely used in Australia. They have common elements involving the dissection of a superficial and deep scleral flap to create an intra-scleral lake, removal of the juxtacanalicular tissue, and a Descemet's window. They can be performed after a trabeculectomy has failed.

Viscocanalostomy involves removal of the inner wall endothelium of Schlemm's canal as well as the juxtacanalicular tissue, the normal site of outflow resistance and the superficial flap is closed with 10-0 monofilament nylon sutures that are applied loosely.

During canaloplasty, the entire circumference of Schlemm's canal is dilated and extended with a viscoelastic compound, followed by placement of 10/0 polypropylene sutures in the canal under tension.

With sclerectomy, the Schlemm's canal was de-roofed and the corneal stroma was excised down to Descemet's membrane so that the aqueous humour percolates through the thin remaining trabeculo-Descemet membrane. Deep sclerectomy can also be performed with a cylindrical collagen drainage device placed radially in the centre of the deep sclerectomy dissection.

Aqueous/tube shunt implantation:

Aqueous shunts or tube shunts are devices that create an alternate path for the aqueous humour to leave the anterior chamber of the eye and lower IOP. In general, a tube is implanted into the anterior chamber of the eye that drains through a plate attached to the sclera and is covered by the eyelid. The fluid that collects is then absorbed into the bloodstream and transported out of the eye cavity. This procedure is usually considered a last-line procedure in patients with advanced disease. Therefore, aqueous/tube shunt implantation is unlikely to be an appropriate comparator for MIGS stent implantation in this population. Insertion of aqueous/tube shunts is reimbursed under MBS item numbers 42752 (insertion) and 42755 (removal).

Rationale

There are two types of MIGS stent implantation procedure currently being reviewed for MBS funding: trabecular bypass MIGS stent implantation (this application) and suprachoroidal MIGS stent implantation (MBS application 1496). PASC advised that suprachoroidal MIGS should be an additional comparator to trabecular bypass MIGS for all three populations. Additionally, any available data to compare the effectiveness of the three trabecular bypass stents should be included in the report.

There are five RCTs investigating effectiveness of combined trabecular bypass MIGS and cataract surgery, compared with cataract surgery alone. There is therefore likely to be sufficient evidence to inform effectiveness of trabecular bypass MIGS in population 1.

Lack of evidence for population 2 has already been highlighted.

The two RCTs investigating effectiveness of trabecular bypass MIGS in phakic patients (population 3) compared trabecular bypass MIGS with topical hypotensive medication (Fea et al. 2014; Vold et al. 2016). This comparator is inappropriate for this population, based on the clinical algorithm. Thus, the effectiveness of trabecular bypass MIGS may need to be assessed using indirect evidence.

Outcomes

Patient relevant outcomes

Clinical Effectiveness: Rate of vision impairment/loss, proportion of vision impairment/loss, time to vision impairment/loss, mean IOP reduction from baseline, proportion of patients with IOP reduction $\geq 20\%$, proportion of patients with IOP ≤ 18 mmHg, time to increase in IOP, change in the number of ocular hypotensive medications, proportion of patients on medication quality of life (effect on daily living activities, e.g. driving, walking, and reading), health-related quality of life (psychological burden due to fear of blindness, social withdrawal, and depression).

Safety: Intraoperative complications, post-operative ocular complications, secondary surgical interventions, corrected distance visual acuity, visual field mean deviation.

Healthcare system

Cost-effectiveness Cost, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio.

Financial implications Number of patients suitable for treatment, number of patients who have successful procedure, number of patients who require additional treatment (medical or surgical).

Clinical management algorithm with and without MIGS stent implantation for the identified populations

The clinical management algorithm for patients with suspected POAG, showing treatment options with and without MIGS stent implantation for patients with mild disease through progression to advanced disease are shown in Figure 1. The algorithm was adapted from the NHMRC Guidelines *for the screening, prognosis, diagnosis, management and prevention of glaucoma* (NHMRC 2010).

The objective of glaucoma management is to provide a significant and sustained decrease in IOP to minimise the risk of progression (i.e. visual field loss), which impacts on the patient's QoL.

For the majority of POAG patients, topical hypotensive medication represents the first-line of therapy as they represent the least invasive treatment option. Patients will initiate with a single topical medication, and the dosing frequency and number of therapies will increase, as required, in order to maintain a target IOP. In patients with cataracts requiring surgery, concurrent MIGS stent implantation (either suprachoroidal or trabecular bypass) offers another option for lowering IOP.

As the condition progresses, hypotensive medication may become less efficacious, or patients may become non-compliant. For such patients, surgical treatment options are considered.

Laser trabeculoplasty is usually considered as the first procedure in patients where IOP cannot be adequately managed with medication alone. MIGS stent implantation is also considered to be an alternative treatment for patients who have had previous cataract surgery at this stage. As the natural lens takes up more space in the eye, there is a risk that surgical procedures may damage the natural lens. As there is no such risk in pseudophakic patients who have had cataract surgery, MIGS is a viable alternative to laser trabeculoplasty.

Following laser trabeculoplasty, more invasive surgical treatment options, known broadly as 'filtering' surgeries, may be considered. The most common first invasive procedure is trabeculectomy. In phakic patients who have no history of cataracts and still have their natural lens, MIGS stent implantation is considered to be a viable alternative option at this stage. In these patients trabeculectomy could still be performed after the MIGS stent implant has failed.

Sclerectomy, viscocanalostomy and canaloplasty are not widely used in Australia but may offer further options to patients in whom all previous treatments have failed. The last line of treatment is aqueous/tube shunt implantation. These surgeries are generally reserved for patients with advanced disease.

In combining populations 2 and 3 in the assessment, the appropriate clinical management algorithm (for the combined population) will be that shown for population 2 in Figure 1 (if 'conservative therapies' exclude laser trabeculoplasty), or population 3 if it includes laser trabeculoplasty.

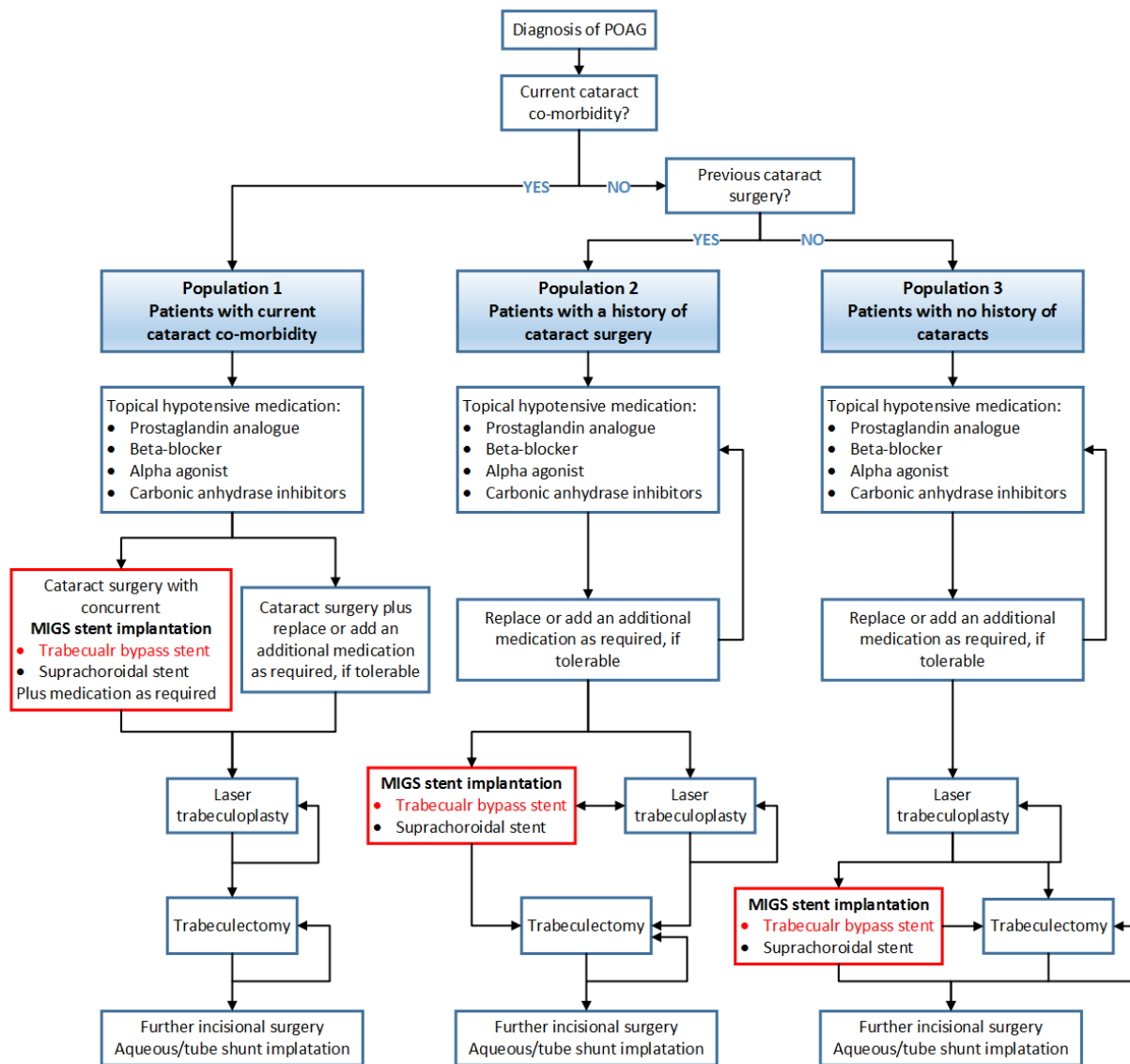


Figure 1 The clinical management algorithm for patients with POAG, showing treatment options with and without trabecular bypass MIGS stent implantation for patients with mild to moderate disease through progression to advanced disease

Source: NHMRC Guidelines: *For the screening, prognosis, diagnosis, management and prevention of glaucoma* (NHMRC 2010)

The addition of trabecular bypass MIGS as a treatment option is shown in red for all three populations

IOP = intraocular pressure; MIGS = micro-invasive glaucoma surgery; POAG = primary open-angle glaucoma

Proposed economic evaluation

The applicant has predicted a claim of superiority for comparative effectiveness, and inferiority for comparative safety, for trabecular bypass MIGS plus cataract surgery (compared with cataract surgery alone) in population 1. The applicant has also predicted a claim of at least non-inferiority in terms of comparative clinical effectiveness and safety for trabecular bypass MIGS (plus standard of care), compared with laser trabeculoplasty (plus standard of care) in population 2. The predicted claim for population 3 is for inferior comparative effectiveness and superior comparative safety of trabecular bypass MIGS over trabeculectomy. On the basis of these claims, PASC advised the appropriate type of economic evaluation would be either a cost-effectiveness or cost-utility analysis.

PASC considered that a comparison between the three different trabecular bypass MIGS stents, and between the trabecular bypass and suprachoroidal MIGS stent implantation procedures, be included

in the submission-based assessment.. If the evidence suggests the different types of MIGS stents are equivalent, a cost-minimisation approach would be appropriate.

The Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee⁴ outline how to structure the decision analytic model underpinning the proposed economic evaluation, which is informed by the final structure of the PICO agreed to by PASC.

Proposed item descriptor

Trabecular bypass MIGS stent implantation has been performed in Australia for the last 3–4 years and has been funded under MBS item number 42758 (goniotomy). However, an MBS review determined that item 42758 was never intended to cover implantation of MIGS stents, and an amendment explicitly excluding this procedure was included in the item from 1 May 2017. This MSAC application is seeking a new MBS item for delivery of trabecular bypass MIGS stent devices in the nominated patient populations (Table 2).

The cost of micro-bypass stent prostheses is not included in the MBS fee. Prostheses are funded through the Prostheses List.

The implantation procedure would be performed once per eye (maximum two procedures per patient), as the stents are designed to last a lifetime. However, they may need repositioning or removal at a later date.

Differences in duration and complexity of the procedure when performed as a ‘stand-alone procedure’ (compared to being performed ‘in conjunction with cataract surgery’) needs clarification and the costs justified. These procedures may require separate MBS item numbers, if costs vary.

The applicant advised that the total service fee must account for other aspects of the procedure (broader than the surgeon’s time), such as preparation time, clinic overheads, observation and post-operative recovery time. There is an economy of scale in performing MIGS implantation in conjunction with cataract surgery, which is recognised by application of the MBS Multiple Services Rule.

The proposed MBS fee for repositioning and removal of the stent is the same as for its insertion, and PASC considered that this needs justification.

Potential for leakage should also be addressed. PASC noted the concern that, given only 20% of patients with cataracts have increased IOP, MIGS may be performed prophylactically in patients requiring cataract surgery. Therefore, the risk that more procedures may be performed than actually required, needs to be considered.

The three trabecular bypass MIGS stent devices that are relevant to the treatment of patients with mild-to-moderate POAG, with or without cataracts, are listed on the Prostheses List (Billing codes: iStent trabecular micro-bypass stent system RQ072, iStent inject system RQ075, Hydrus microstent OQ002).

⁴ Available from URL: <<http://www.msac.gov.au/internet/msac/publishing.nsf/Content/assessment-groups>>, accessed 16 March 2017.

Prostheses List benefits for glaucoma drainage devices range from \$800 to \$1,600 each. PASC recommended that the difference between usage of these devices (and their impact on the treatment populations) be investigated further.

Table 2 MBS item descriptors for trabecular bypass MIGS stent implantation

Category 3 – THERAPEUTIC PROCEDURES	
MBS item number	
	<p>GLAUCOMA, implantation of a micro-invasive glaucoma surgery stent system into the trabecular meshwork, in patients diagnosed with primary open-angle glaucoma currently treated with ocular hypotensive medication. Can be delivered as a stand-alone procedure or in conjunction with cataract surgery.</p> <p>When delivered as a stand-alone procedure, pseudophakic patients must have inadequate IOP control with maximally-tolerated ocular hypotensive medication, and phakic patients must have failed or be likely to fail laser trabeculoplasty, or be contraindicated for this procedure</p>
	Multiple Services Rule
	Fee: \$699.45 [approximate fee based on MBS item 42758 – to be determined]
MBS item number	
	<p>GLAUCOMA, repositioning or removal of, a micro-invasive glaucoma surgery stent system from the trabecular meshwork</p>
	Multiple Services Rule
	Fee: \$699.45 [approximate fee based on MBS item 42758 – to be determined]

The MBS item descriptor for filtering surgeries restricts the intervention to glaucoma patients “where conservative therapies have failed, are likely to fail, or are contraindicated”. If populations 2 and 3 are combined, the patient population likely to access stand-alone MIGS stent implantation through the MBS are those otherwise eligible for incisional filtering surgeries. Thus, the wording for the proposed MBS item descriptor could be amended to read: “When delivered as a stand-alone procedure, conservative therapies must have failed, be likely to fail, or be contraindicated”

The applicant has indicated that a comprehensive cost analysis of the proposed service will be undertaken during development of the submission based assessment and that the fee would be expected to be similar to the current fee for MBS item number 42758 (goniotomy). Advice from the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) suggests the fee for this service (\$699.45, as for goniotomy) is a reasonable representation of the true cost of delivering the proposed service. A response to a targeted consultation survey on MSAC Application 1483 indicated the proposed service should be rebated at a rate comparable to goniotomy (MBS item number 42758).

A second response to the consultation survey indicated the proposed fee is possibly higher than the procedure warrants, whereas the Australian and New Zealand Glaucoma Society (ANZGS) stated the proposed fee is already lower than in other developed countries for insertion of the trabecular device.

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