

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1764 – Micro-bypass glaucoma surgery device implantation into the suprachoroidal space as a standalone procedure in patients with open angle glaucoma

Applicant: iStar Medical

Date of MSAC consideration: 4-5 April 2024

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 public funding of micro-bypass glaucoma surgery (MBGS) device implantation into the suprachoroidal space as a standalone procedure in patients with open angle glaucoma (OAG), for whom conservative therapies have failed, are likely to fail or are contraindicated was received from iSTAR Medical by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the amendment of the existing Medicare Benefits Schedule (MBS) item to add micro-bypass glaucoma surgery device implantation into the suprachoroidal space as a standalone procedure. MSAC considered the insertion of a suprachoroidal stent had at least non-inferior effectiveness compared to the insertion of a stent into the trabecular meshwork. MSAC noted there were limited long-term safety data, however considered that there was no evidence to suggest the safety concerns with the previously withdrawn suprachoroidal device applied to other devices that differ in structure and size, and safety is routinely evaluated through regulatory processes and registries. MSAC considered the standalone insertion of a suprachoroidal stent will provide another option for these patients, and that these stents are already used in conjunction with cataract surgery. MSAC considered the cost-minimisation analysis against trabecular stents showed the insertion of a suprachoroidal stent was acceptably cost-effective. There will probably be some patients receiving a suprachoroidal stent who would not have received a trabecular stent, although the financial impact from this would likely be minimal and was acceptable. MSAC supported the removal of the training requirement from the MBS item descriptor as the specified committee had not been established, and the addition of an explanatory note to relevant MBS items to clarify that suprachoroidal and supraciliary stents are interchangeable terms.

MSAC's supported revised MBS item descriptor is below (Table 1).

Table 1 MSAC’s supported revised MBS item descriptor

Category 3 – Therapeutic procedures
MBS item 42504 Glaucoma, implantation of a micro-bypass surgery stent system into the suprachoroidal space or trabecular meshwork, if conservative therapies have failed, are likely to fail, or are contraindicated
Fee: \$331.05 75% benefit: \$248.30 85% benefit: \$281.40
<u>Explanatory note:</u> The suprachoroidal and supraciliary spaces are contiguous and are potential spaces opened by surgery to allow drainage of aqueous humour, and the terms are used interchangeably.

Source: MSAC.

Consumer summary
<p>This was an application from iStar Medical requesting Medicare Benefits Schedule (MBS) listing of micro-bypass glaucoma surgery (MBGS) device implantation into the suprachoroidal space as a standalone procedure in patients with open angle glaucoma.</p> <p>Glaucoma is an eye condition where people lose peripheral vision and may lose their vision completely if it is not treated. The eyeball is filled with a fluid, and increased pressure inside the eye increases a person’s risk of glaucoma. Surgery can be used to lower the pressure inside the eyeball in patients with glaucoma. This surgery involves placing a small device called a stent inside the eye to help fluid in the eye to slowly drain away, which lowers the pressure. This application proposed funding surgery to implant a stent into a part of the eye called the suprachoroidal space. It is intended to be used in patients for whom glaucoma eye drops don’t work. A similar surgery is already publicly funded under MBS item 42504 for implanting a device into a different place in the eye, called the trabecular meshwork. Inserting a suprachoroidal stent is also already publicly funded but only as part of other eye surgery, not as a standalone procedure. The suprachoroidal stents that could be inserted using this surgery would include the applicant’s “MINIject” stent.</p> <p>A previous application to MSAC that proposed funding this surgery was withdrawn after safety concerns. While there was limited long-term safety data, MSAC considered the evidence showed no reason to suggest the safety concerns with the previously withdrawn suprachoroidal device applied to other devices that differ in structure and size. MSAC also considered that safety is ensured by regulatory processes and registries, and so on balance this surgery was acceptably safe.</p> <p>The evidence also showed that inserting a suprachoroidal stent was at least as good as a trabecular stent in reducing pressure in the eye. The applicant proposed this surgery should cost the same as the existing surgery to implant a trabecular stent, and MSAC considered given it was at least as effective, that the proposed surgery was good value for money.</p> <p>The applicant proposed that suprachoroidal stents would only replace trabecular stents, and no extra patients would receive a suprachoroidal stent so there would be no net cost to the MBS to add this surgical option. However, MSAC considered that suprachoroidal stents would offer another option for patients, probably including some patients who would not have received a trabecular stent (such as patients who have trabecular scarring). But MSAC considered that the increased cost to the MBS would likely be minimal, and so advised the cost to the MBS was acceptable.</p> <p>MSAC noted that the words ‘supraciliary’ and ‘suprachoroidal’ (to describe the part of the eye) were both being used in the application documents to describe this surgery. On the Australian Register of Therapeutic Goods the MINIject device is described as ‘supraciliary’, whereas MBS items say ‘suprachoroidal’. MSAC considered that the supraciliary space and the suprachoroidal space run into each other, so the two words effectively mean the same thing. To avoid confusion, MSAC also recommended adding an explanatory note to the MBS to clarify</p>

Consumer summary

(for this and other relevant MBS items) that the suprachoroidal and supraciliary spaces of the eye are continuous. This surgery can therefore be used for the insertion of a suprachoroidal or supraciliary stent.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported funding the standalone insertion of a suprachoroidal stent on the MBS. MSAC considered the insertion of a suprachoroidal stent to be safe, at least as effective as the existing surgery, good value for money, and to have minimal financial cost to the MBS. It will also provide another option for patients.

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

MSAC noted that this application requested an amendment to the existing Medicare Benefits Schedule (MBS) item 42504 to add micro-bypass glaucoma surgery (MBGS) device implantation into the suprachoroidal space as a standalone procedure in patients with open angle glaucoma for whom conservative therapies have failed or are likely to fail. MSAC noted that previous MSAC application 1541 had originally included suprachoroidal stents as well as trabecular stents, although suprachoroidal stents were withdrawn after the CyPass device was withdrawn from the market over safety concerns. Standalone stent implantation was supported by MSAC for insertion into the trabecular space only, and this was therefore the proposed comparator in application 1764. MSAC noted that insertion of a stent into the suprachoroidal space is already publicly funded under MBS item 42705, for insertion in association with cataract surgery (and removal if required, using MBS item 42505), so the device is already on the Prescribed List (PL).

MSAC noted that glaucoma is an eye condition most commonly treated through treatments to reduce intraocular pressure (IOP), which is the only known modifiable risk factor for glaucoma.

MSAC noted consultation input from 3 professional organisations, and 4 individuals (of whom all were medical specialists). MSAC noted that MBGS procedures can be highly specialised techniques and are therefore likely to be less available in rural and remote areas, which is likely to impact on patient access and equity. MSAC also considered that accessibility for populations much at risk of glaucoma, including First Nations peoples, was an important equity issue with this application.

MSAC noted inconsistency in use of the terms 'suprachoroidal' and 'supraciliary' to describe anatomical areas where these MBGS devices are inserted: the applicant's MINInject device is described on the Australian Register of Therapeutic Goods (ARTG) as a supraciliary device, however the applicant proposed stent insertion would be supported through amending the MBS item descriptor to add 'suprachoroidal', which is also the term used in other MBS items. MSAC noted ESC had considered 'supraciliary' may be a subset of 'suprachoroidal', however the two spaces are in fact continuous, so MSAC considered the two anatomical terms were interchangeable. MSAC advised the term "suprachoroidal" was more appropriate to use in the MBS item descriptor for consistency with existing MBS items, and that clarification of this anatomical point would be improved by adding an explanatory note to relevant MBS items to clarify that suprachoroidal and supraciliary are interchangeable terms, to clarify which types of device can be inserted using the relevant MBS items. MSAC noted the Department would consult the sector on the wording of the explanatory note. In addition, MSAC agreed with the proposal from ESC and the Department to delete reference to the Conjoint Committee for the Recognition

of Training in Micro-Bypass Glaucoma Surgery, as the specified committee had not been established.

MSAC noted the evidence presented by the applicant was specific to the MINject brand of suprachoroidal stent, however it considered the appropriate addition to the MBS item descriptor should be device-agnostic, because in MSAC's view it was reasonable to assume generalisability of the evidence to other suprachoroidal stents.

MSAC noted ESC had raised uncertainty about the clinical need and the population in whom suprachoroidal stents should be used. MSAC considered that the appropriate use of suprachoroidal stents, whether used in preference to other stents or not, would be determined by the patient and clinician together, and these stents were likely to provide an alternate option. For example, MSAC considered a suprachoroidal stent may be used in patients who have trabecular scarring or in whom the trabecular meshwork is physically inaccessible, where inserting a stent into the trabecular meshwork is not possible. MSAC considered that if trauma or scarring could be avoided, this would also allow more surgical options to remain for patients in the future, constituting a further potential advantage. MSAC noted the applicant in its pre-MSAC response advised that the insertion of multiple stents was possible although highly unlikely and not current practice – and that in that situation the alternative to inserting an additional stent may be trabeculectomy. MSAC noted the applicant also considered suprachoroidal stents were unlikely to replace trabecular stents as the most common procedure. Overall, MSAC was satisfied that there was sufficient clinical place and need for suprachoroidal stents in addition to trabecular stents, mainly because they will provide another option for patients. MSAC also considered that the clinical place for suprachoroidal stents in these patients may develop over time.

Regarding clinical safety, MSAC noted that the evidence showed adverse events from MINject use were infrequent and could be mitigated, with anterior chamber inflammation being the main safety risk occurring in approximately 30% of patients. MSAC considered that although there was little long-term safety data for MINject (data were limited to 2-3 years), there was also no evidence suggesting corneal endothelial cell loss as had been observed with the suprachoroidal CyPass device, leading to its withdrawal from the Australian market. MSAC noted that the MINject stent differed in structure and length from the CyPass stent, and considered the insertion of MINject will not necessarily lead to comparable adverse events despite insertion into a similar space. MSAC considered that device safety was ensured through existing regulatory processes, including registries. MSAC further noted the insertion of a suprachoroidal stent is already publicly funded in Australia in conjunction with cataract surgery. Overall, MSAC advised that the safety of inserting a suprachoroidal stent was non-inferior compared to inserting a trabecular stent.

Regarding clinical effectiveness, MSAC noted that the evidence showed insertion of the MINject resulted in a clinically significant reduction in IOP at 6, 12 and 24 months. However, MSAC noted a lack of direct head-to-head comparison studies between MINject and the applicant-developed assessment report (ADAR)'s nominated comparator of the iStent (Glaukos; one brand of trabecular stent), and that the ADAR instead used a naïve unanchored indirect treatment comparison (ITC) to estimate the relative effectiveness of the insertion of suprachoroidal stents compared to trabecular stents. MSAC noted the trial populations were more homogenous for the intervention than the comparator, stemming from differences in study design and eligibility criteria. MSAC considered these compromised the validity of the ITC analysis, and agreed with ESC that the evidence supported a claim of at least non-inferior effectiveness.

MSAC noted the applicant proposed the fee for the insertion of a suprachoroidal stent be the same as the current fee for the insertion of a trabecular stent, and considered this was reasonable.

MSAC noted ESC had considered a cost utility analysis (CUA) or cost-effectiveness analysis (CEA) would have been preferred over the ADAR's cost-minimisation analysis (CMA) given the applicant claimed superior safety and effectiveness. However, MSAC considered that as safety and effectiveness were more reasonably non-inferior, the cost-minimisation analysis was sufficient for decision-making. MSAC noted the ADAR reported an expected net saving of \$240.58 per MINInject procedure (per patient over 2 years), based on reduced costs from lower usage of medications and eyedrops to reduce intraocular pressure and manage ocular surface disease (OSD). MSAC agreed with ESC that the economic evaluation was somewhat uncertain due to uncertainty over the level of evidence informing the analysis, and that some of the inputs were speculative (in particular, the claimed cost-offsets from reduced OSD medication were highly uncertain). However, MSAC considered that higher level evidence was unlikely to be forthcoming and noted that overseas studies have shown MINInject to be cost-effective. Overall, MSAC advised that the insertion of a suprachoroidal stent was acceptably cost-effective.

MSAC noted that a market share approach was used for the utilisation and financial estimates. MSAC noted the estimated low initial usage and projected increase in usage, with the ADAR's analyses showing no net cost to the MBS as suprachoroidal stents would only ever replace trabecular stents. MSAC considered that the main uncertainty was whether some patients may receive multiple stents in the same eye (a supraciliary procedure and then a trabecular procedure, or the reverse), in which case there would be a net increase in utilisation and therefore cost to the MBS. MSAC noted that the applicant's pre-MSAC response stated that this situation would be highly unlikely and is not current practice. MSAC considered that there will likely be a small amount of non-replacement (i.e., additional) use, for example in patients with trabecular scarring who could receive a suprachoroidal stent but could not have received a trabecular stent under the comparator. MSAC considered there was value for patients in having another option available to them, and that while the non-replacement use would come at an additional cost to the MBS, advised this would likely be minimal and was acceptable. MSAC also considered that the 75% (in-hospital) benefit was more appropriate, given the high rate of MBGS device implantation performed in-hospital. Given the uncertainty around estimated utilisation, although service volumes were anticipated to be small MSAC recommended utilisation be monitored.

4. Background

To date, one prior application has been considered by the Medical Service Advisory Committee (MSAC) for a standalone MBGS procedure for insertion of a stent into the suprachoroidal space.

Prior applications regarding the implantation of MBGS devices are summarised in Table 2, including dates, indications and MSAC recommendations. Most relevant to the current application is MSAC Application 1541: 'Micro-bypass glaucoma surgery device implantation in trabecular meshwork or suprachoroidal space as a standalone procedure in patients with open angle glaucoma' (November 2018). The first 1541 submission (for standalone insertion of a stent into the suprachoroidal space or trabecular meshwork) was not supported by MSAC in November 2018, with MSAC listing the following concerns: eligibility criteria and high leakage risk to other populations, poor comparative safety data, poor comparative efficacy, and unsatisfactory economic assessment. A resubmission of the 1541 application for standalone insertion of a stent into the trabecular meshwork excluded suprachoroidal minimally invasive glaucoma surgery (MIGS)/MBGS due to the withdrawal of the suprachoroidal MIGS CyPass stent from the Australian market due to safety concerns, and standalone insertion of a trabecular stent was supported by MSAC in August 2019.

Under Medicare Benefits Schedule (MBS) item 42705, the insertion of a stent into the suprachoroidal space is publicly funded in association with cataract surgery (and removal if required, using item 42505).

Table 2 Relevant previous MSAC applications regarding the use of micro-bypass glaucoma surgery device implantation in patients with open angle glaucoma

Application number	Date of MSAC consideration	Indication	MSAC advice
1483	November 2017	Usage of TB MBGS as a standalone procedure and combination with cataract surgery in patients with OAG	Supported only in combination with cataract surgery (item 42705)
1496	November 2017	Usage of SC MBGS as a standalone procedure and combination with cataract surgery in patients with OAG	Supported only in combination with cataract surgery (item 42705)
1541	November 2018	Resubmission of the unsuccessful components of applications 1483 and 1496 for MBGS device implantation in TB meshwork and SC space as a standalone procedure in patients with OAG	Not supported: unclear eligibility criteria and high leakage risk to other populations, poor comparative safety data, poor comparative efficacy and unsatisfactory economic assessment
1541 resubmission	August 2019	Resubmission of 1541 for MBGS device implantation in TB meshwork as a standalone procedure in patients with OAG	Supported and MBS listed in May 2020 (MBS item 42504)

Abbreviations: OAG = open angle glaucoma, MBGS = micro-bypass glaucoma surgery, MSAC = Medical Services Advisory Committee; TB = trabecular, SC = suprachoroidal

Source: Compiled for the commentary

5. Prerequisites to implementation of any funding advice

Both MINject® and MINject® S (next generation device) are Therapeutic Goods Administration (TGA) approved and included on the Australian Register of Therapeutic Goods (ARTG; ID 400268). The effective ARTG listing date for MINject® was 28 November 2022, and a 9D amendment notice to include MINject® S was dated 12 September 2023. MINject is an ARTG medical device included in Class IIb. The intended purpose of the MINject device listed in ARTG ID 400268 is as an integrated system for MIGS. The only difference between MINject® and the MINject® S is the material of the sheath of the delivery tool. The implants of both devices are identical, as are the procedures.

6. Proposal for public funding

This applicant developed assessment report (ADAR) submission seeks to support the MINject delivery system for use in MBGS device implantation into the suprachoroidal space as a standalone procedure in patients with OAG, for whom conservative therapies have failed, are likely to fail or are contraindicated.

The proposed funding arrangement is via the MBS, by extending the existing item 42504 to include phrasing regarding the implantation of the MBGS device into the suprachoroidal space (Table 3). The proposed fee is the same as the existing 42504 fee, given the similar cost

associated with the insertion of MINject compared with the comparator during MBGS standalone surgery.

Table 3 Proposed item descriptor for implantation of MINject (or other relevant MBGS devices) via the suprachoroidal space or trabecular meshwork during standalone micro-bypass glaucoma surgery

Category 3 – Therapeutic procedures
MBS item 42504 Glaucoma, implantation of a micro-bypass surgery stent system into the <u>suprachoroidal space</u> or trabecular meshwork, if: (a) conservative therapies have failed, are likely to fail, or are contraindicated; and (b) the service is performed by a specialist with training that is recognised by the Conjoint Committee for the Recognition of Training in Micro-Bypass Glaucoma Surgery
Fee: \$329.40 <u>\$331.05</u> <u>75% benefit: \$248.30</u> <u>85% benefit: \$281.40</u>

Source: Table 3 of ADAR submission. Underline font indicates the ADAR’s proposed addition to existing MBS item 42504.

Note: The proposed fee was amended during the evaluation to reflect November 2023 indexation, although the economic and financial analyses presented use the October 2023 fee (\$329.40).

7. Population

Table 4 summarises the population, intervention, comparator and outcome (PICO) criteria presented in the current ADAR submission. The target population was defined as ‘patients with glaucoma requiring implantation of a MBGS stent system into the suprachoroidal space, if: (a) conservative therapies have failed, are likely to fail, or are contraindicated; and (b) the service is performed by a specialist with training that is recognised by the Conjoint Committee for the Recognition of Training in Micro-Bypass Glaucoma Surgery.

The population specified is identical to existing item 42504, with the addition of suprachoroidal MBGS as a standalone procedure for patients with OAG where conservative therapies (e.g. antihypertensive medication, laser therapy) have failed. Regarding unmet need, the applicant argued that the extension of current guidelines to include suprachoroidal implantation of MBGS devices would better allow surgeons to select the most appropriate procedure according to their preferences and their patients’ needs; however, the applicant failed to establish whether the current clinical management pathway (i.e. trabecular MBGS) was insufficient and did not provide clinical expert opinion regarding the need for suprachoroidal MBGS.

The assessment group note that there remains some uncertainty as to whether the defined population may include patients that have been unable to access a trabecular stent (e.g. iStent) and/or whether a patient could potentially receive both a trabecular stent and a suprachoroidal stent. Additionally, in cases where a stent fails to produce a satisfactory patient outcome, whether it would be removed and either replaced by another stent or requiring the patient to undergo a more invasive therapy (e.g. trabeculectomy). If any of the above scenarios are realistic, the MBS may incur greater net costs due to a potentially larger population than currently catered for under the existing device.

Further clarity is also required regarding the positioning of the device within the clinical management pathway. The ADAR suggests that MINject will meet clinical needs not currently covered by the trabecular stent. This raises the question of whether there would overall be a shift to the suprachoroidal delivery because of superiority or whether it just provides an equivalent but alternative option to the trabecular delivery.

Table 4 PICO criteria for assessing MINject versus iStent for use in standalone micro-bypass glaucoma surgery

Component	Description
Population	Patients with glaucoma requiring implantation of a MBGS stent system into the suprachoroidal space, if: (a) conservative therapies have failed, are likely to fail or are contraindicated; and (b) the service is performed by a specialist with training that is recognised by the Conjoint Committee for the Recognition of Training in Micro-Bypass Glaucoma Surgery
Intervention	MINject® micro-bypass surgery device, which is inserted into the suprachoroidal space during MBGS.
Comparator	iStent® (Glaukos) MBGS stent system (inserted via the trabecular meshwork)
Outcomes	Safety: AE, including ocular SAEs (number, % of patients) related to the device or surgical procedure Effectiveness: Change from baseline in IOP (mm Hg, % reduction) Change from baseline in the mean number of IOP-reducing medications used Healthcare system outcomes: Resource used to implant the stent system (e.g. professional services, prostheses, post-operative consultations, AEs)
Systematic review questions: What is the safety, effectiveness and cost-effectiveness of MINject compared to iStent in standalone MBGS (also called MIGS)?	

Abbreviations: AE = adverse event; IOP = intraocular pressure, mm Hg = millimetres of mercury, MBGS = micro-bypass glaucoma surgery; SAE = serious adverse event

Source: Table 2 of ADAR submission

8. Comparator

The comparator selected for assessment in the ADAR submission was iStent® (Glaukos), an alternative micro-bypass surgery stent system implanted via the trabecular meshwork. The applicant reasoned that the iStent device, used within the same 42504 standalone code, is the most appropriate comparator to MINject compared with other procedures such as selective laser trabeculoplasty and trabeculectomy, as the iStent belongs to the same ‘MBGS’ class as MINject and has a similar class level of safety and efficacy. Furthermore, iStent currently represents the most-used MBGS device in Australia. Despite the applicant's assertion that a clinical expert survey was conducted to corroborate the choice of comparator, details regarding the survey's design and findings were not provided, meaning the assessment group could not validate the applicant's conclusions. As such, there remains some uncertainty as to whether iStent should have been selected as the sole comparator in the ADAR submission. The exclusion of any additional relevant comparators may have reduced the amount of direct evidence available to comprehensively assess the intervention.

9. Summary of public consultation input

Consultation input was welcomed from four (4) professional organisations, and eight (8) individuals, seven of whom were medical specialists and one a researcher.

The organisations who submitted input were:

- Private Healthcare Australia
- Australian Society of Ophthalmologists Ltd (ASO)
- Medical Devices and Human Tissue Advisory Committee (MDHTAC) Ophthalmic Expert Clinical Advisory Group (ECAG) (*Targeted*)

- Royal Australian and New Zealand College of Ophthalmologists (RANZCO) (*Targeted*)

All feedback received was supportive of the application.

Benefits

Traditional glaucoma treatments often involve medications with potential side effects or invasive surgical procedures.

- The MINject implant is inserted into the supraciliary space of the eye and gives surgeons another option where trabecular meshwork devices are not appropriate, rather than resorting to more invasive filtering surgeries.
- There are no other supraciliary devices currently available in Australia.
- MINject has proven efficacy far superior to the comparator for glaucoma surgery, with a similar safety profile. It has the safety advantage of being bleb-free, unlike devices that target the subconjunctival space which create a filtering bleb.
- The MINject stent minimises the need for extensive surgery while effectively addressing intraocular pressure, with a short procedure time, fast patient recovery time, minimal follow-ups, and fewer complications in comparison with a more invasive glaucoma filtering procedure.
- Given they address different physiological pathways, failure of one type of MBGS stent may result in a second procedure utilising the alternative (supraciliary) pathway. Trabecular stents are most likely to remain the initial MBGS procedure.
- The minimally invasive nature of the stent procedure may lead to shorter hospital stays and quicker rehabilitation promoting a more efficient healthcare system.
- The procedure is more cost effective long term than trabeculectomy.
- By allocating public funds to cover the costs of glaucoma stent surgery, access to treatment is expanded and provides greater equity of access.
- Reduced burden from eye drops and need for carers to administer

Disadvantages /Implementation Issues

- Cost of procedure.
- As with all glaucoma operations, risks of surgical failure, hypotony, infection, scarring and bleeding.
- Longer term outcomes are not yet known as this procedure is relatively new.

Other Feedback

Suprachoroidal stents are very different to trans-trabecular stents, in that in that they create an entirely new pathway for intraocular fluid drainage and lowering of intraocular pressure.

Feedback was mixed regarding adding suprachoroidal stents to the current MBS descriptor for trabecular stents. On one hand it was noted that adding "suprachoroidal space" to the current descriptor would bring additional clarity to surgeons seeking to use the MBS 42504 code for standalone MINject implantation, and on the other it was noted that suprachoroidal stents could warrant their own MBS item number because they are used differently and have different complication profiles compared with trabecular stents.

The number of procedures using suprachoroidal stent techniques is not expected to be high, and would be limited to very experienced glaucoma sub-specialists who will use the stents for indications where other more predictable techniques are contra-indicated.

There would be no difference to standard of care before or after using the MINject implant in a standalone procedure under MBS code 42504 compared with other MIGS implants such as iStent or Hydrus currently claimed under this code.

In terms of associated consumables during surgery, procedure duration and number of follow-up appointments, MINject has a similar resource intensity as the other MBGS devices whose insertion is already funded.

10. Characteristics of the evidence base

Identification of the evidence base

To support clinical evaluation of the relative effectiveness and safety of MINject and the comparator iStent when used in standalone MBGS, a systematic literature review (SLR) was undertaken to identify relevant studies for MINject or iStent used for standalone MBGS. The search included key databases (EMBASE, Medline, Cochrane Library, Science Direct, ClinicalTrials.gov) as well as the applicant’s databases.

A summary of relevant trials identified in the literature for MINject and iStent is provided in Table 5. A total of 4 MINject and 7 iStent studies were identified. The MINject trials consisted of 4 identically designed, prospective, single-arm trials (labelled STAR-I to STAR-IV), each enrolling between 21 and 31 patients. In contrast, the iStent trials were a collection of single-arm trials and a single case series study, enrolling between 10 and 100 patients. All trials monitored and reported the key efficacy outcomes (change from baseline in IOP and usage of IOP-lowering medications between 6 and 24 months) as well as safety outcomes.

The assessment group noted that the SLR searches covered a range of resources, including online databases, the applicant’s databases, and clinical trial registries. The applicant mentioned that ‘attempts were also made to source unpublished or grey literature from internet searches and review of articles’; however, no further details of the results of these efforts were described, and a grey literature search was not stated as part of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 10 of the ADAR). Also, conference proceedings did not appear to have been examined.

The eligibility criteria appeared to mirror the submission PICO (see Table 4); however, several limits appear to have been placed during the study selection process including i) language limit of articles published only in the English language, ii) publication source limit of articles published only by peer-reviewed journals and iii) publication type limit of clinical trials only. It is unclear whether these limits may have resulted in relevant studies being missed from the SLR.

Full database search strategies supporting the MINject search and iStent search for the original SLR and its subsequent update were not provided in this submission. The applicant did not provide any information on the SLR data extraction process. The assessment group was thus unable to judge whether the process had been optimal in reducing bias and error.

Table 5 Summary of studies identified for ADAR submission

Trial/study	N	Study design	Population	Intervention	Comparator	Key outcome(s)
MINject						
STAR-I	26	Prospective, single arm	Adults with POAG, SOAG with ≥1 IOP-lowering medications	MINject	NA	Mean change from baseline in IOP (mm Hg) at 6, 12, 24 months Change from baseline in mean number of medications, n at 6, 12, 24 months Adverse events, n
STAR-II	31					
STAR-III	25					
STAR-IV	21					

Trial/study	N	Study design	Population	Intervention	Comparator	Key outcome(s)
iStent						
Voskanyan 2014 ¹	99	Prospective, post market, unmasked	Adults with POAG or SOAG with ≥ 2 IOP-lowering medications	iStent	NA	Mean change from baseline in IOP (mm Hg) at 6, 12, 24 months Change from baseline in mean number of medications, n at 6, 12, 24 months Adverse events, n
Hengerer 2019 ² ; Hengerer 2022 ³	31 patients/ 44 eyes	Prospective, consecutive case series	Adults with POAG, NAG or secondary glaucoma Inadequate response to IOP-lowering medication			
Lindstrom 2020 ⁴	57	Prospective, single arm, single surgeon	Adults with POAG with 1 IOP-lowering medication			
Arnljots 2021 ⁵	14 eyes	Retrospective, interventional case series	Adult with mild to moderate OAG			
Pahlitzsch 2021 ⁶	66	Retrospective, single centre	Adults with POAG which had received iStent			
Katz 2018 ⁷	41	Prospective, randomised, open label*	Adults with OAG on 1–3 IOP-lowering medication			
Ahmed 2020 ⁸	77 (iStent arm)	Prospective, multicentre, randomised, single masked**	Adults with OAG			

Abbreviations: IOP = intraocular pressure, mm Hg = millimetres of mercury, OAP = open angle glaucoma, POAG = primary open angle glaucoma, SOAG = secondary open angle glaucoma

Source: Table 6 of ADAR submission

* Only the 2 (n=41) iStent arm was included in this analysis.

** Only the iStent arm was included in this analysis.

1 Voskanyan L, García-Feijó J, Belda JI, et al. Prospective, unmasked evaluation of the iStent® inject system for open-angle glaucoma: synergy trial. *Adv Ther* 2014;31(2):189-201.

2 Hengerer FH, Auffarth GU, Riffel C, et al. Second-Generation Trabecular Micro-Bypass Stents as Standalone Treatment for Glaucoma: A 36-Month Prospective Study. *Adv Ther* 2019;36(7):1606-17.

3 Hengerer FH, Auffarth GU, Conrad-Hengerer I. iStent inject Trabecular Micro-Bypass with or Without Cataract Surgery Yields Sustained 5-Year Glaucoma Control. *Adv Ther* 2022;39(3):1417-31.

4 Lindstrom R, Sarkisian SR, Lewis R, et al. Four-Year Outcomes of Two Second-Generation Trabecular Micro-Bypass Stents in Patients with Open-Angle Glaucoma on One Medication. *Clin Ophthalmol* 2020;14:71-80.

5 Arnljots TS, Economou MA. Kahook Dual Blade Goniotomy vs iStent inject: Long-Term Results in Patients with Open-Angle Glaucoma. *Clin Ophthalmol* 2021;15:541-50.

6 Pahlitzsch M, Davids AM, Winterhalter S, et al. Selective Laser Trabeculoplasty Versus MIGS: Forgotten Art or First-Step Procedure in Selected Patients with Open-Angle Glaucoma. *Ophthalmol Ther* 2021;10(3):509-24.

7 Katz LJ, Erb C, Carceller Guillamet A, et al. Long-term titrated IOP control with one, two, or three trabecular micro-bypass stents in open-angle glaucoma subjects on topical hypotensive medication: 42-month outcomes. *Clin Ophthalmol* 2018;12:255-62.

8 Ahmed IK, Fea A, Au L, et al. A Prospective Randomized Trial Comparing Hydrus and iStent Microinvasive Glaucoma Surgery Implants for Standalone Treatment of Open-Angle Glaucoma: The COMPARE Study. *Ophthalmology* 2020;127(1):52-61.

Statistical analysis

Given none of the identified trials directly compared MINject with iStent, an indirect treatment comparison (ITC) was undertaken to generate estimates of relative effectiveness.

Outcomes selected to evaluate the relative effectiveness of MINject and iStent included change from baseline in IOP and change from baseline in the mean number of IOP-reducing medications. Reductions in IOP influences both the risk of developing glaucoma and the progression of existing disease; reductions in the usage of IOP-lowering medications indicates better disease management, with quality of life and resource-use benefits. Both endpoints represent objective and consistently reported metrics on which to assess comparative effectiveness; however, the assessment group noted that cross-trial differences in baseline IOP and medication usage will bias relative effect estimates, likely in favour of trials with higher average baseline values, due to there being greater possibility for improvement. Safety outcomes, including adverse events, were also considered.

The applicant opted for a naïve, unanchored ITC. Reported efficacy outcomes from each of the identified trials were meta-analysed using random effects methodology into a single estimate of efficacy for each technology, and indirectly compared via a simple subtraction method (analogous to the Bucher method). Safety outcomes were compared across the 2 sets of studies. Due to the small number of events usually seen with safety outcomes, no statistical comparisons were conducted.

Typically, unanchored-naïve treatment comparisons are associated with a high degree of uncertainty and outcomes presented from such analyses should be interpreted with caution due to the high potential for the comparison to be influenced by factors other than the treatments being compared. For outcomes of the unanchored ITC to be valid, all trials included must be balanced in terms of potential effect-modifying and prognostic factors (assumption of similarity), and there must be no relevant heterogeneity between trial results in pairwise comparisons (assumption of homogeneity). Violation of either assumption will compromise the validity of the analysis.

In an effort to support the comparability of the MINject and iStent studies for use in an ITC, the applicant undertook a 'risk of bias' assessment of each of the studies (using the ROBINS-1 non-randomised study assessment tool preferred for Cochrane Reviews). Furthermore, a qualitative comparison of trial eligibility criteria and a quantitative comparison of baseline characteristics was undertaken. The applicant also stated that an investigation of the potential impact of characteristics that are known treatment-effect modifiers was conducted; however, this was not evident from the submission.

Assessment of evidence base

Risk of bias assessment

Based on the applicant's assessment, all 4 MINject and 6 of 7 iStent trials were considered to have a low risk of bias; however, the assessment group's reappraisal of these studies found that 3 out of 4 MINject trials and 5 out of 7 iStent trials were of a low risk of bias (see Table 6). The assessment group marked down 1 MINject trial and 1 iStent trial as being of moderate risk of bias, and 1 iStent trial was judged to be of a high risk of bias.

GRADE criteria were employed in assessing the evidence used to support the MINject vs iStent ITC. Although the applicant's original assessment concluded that the evidence base was of moderate (⊕⊕⊕⊖) to high (⊕⊕⊕⊕) quality, the assessment group reached the conclusion that there is low (⊕⊕⊖⊖) to high (⊕⊕⊕⊕) confidence in the quality of evidence base used to support the relative efficacy and safety of MINject vs iStent in standalone MBGS procedures.

Table 6 GRADE reassessment of study domains

Assessment criteria	MINIject	iStent	GRADE assessment	
			Applicant	Assessment group
Study design	Single arm, prospective, no special strengths or important limitations	Single arm, 5/7 (71%) prospective, 2/7 (29%) retrospective No special strengths or important limitations	⊕⊕⊕⊖	⊕⊕⊕⊖
Study limitations (risk of bias)	Potential limitations addressed in 'study design' domain		⊕⊕⊕⊕	⊕⊕⊕⊕
Inconsistency of results	Figure 11 of ADAR submission (Figure 1): broadly consistent effect sizes	Figure 11 of ADAR submission (Figure 1): considerable variation in effect estimates, large I ² statistic (n=5): 93.69%	⊕⊕⊕⊕	⊕⊕⊕⊖
Indirectness of evidence	Notable differences between MINIject and iStent trials		⊕⊕⊕⊖	⊕⊕⊕⊖
Imprecision	Considerable limitations		⊕⊕⊕⊖	⊕⊕⊕⊖
Publication bias	Unclear reporting of review process		⊕⊕⊕⊖	⊕⊕⊕⊖

Source: Adapted from Appendix D, Table 47 of ADAR submission

Comparison of trial eligibility criteria

The eligibility criteria of the included trials are summarised in Table 7. The MINIject and iStent trials enrolled comparable patient groups, including adults who mainly had primary open angle glaucoma (POAG) or secondary open angle glaucoma (SOAG) (including pseudoexfoliative glaucoma [PXG] or pigmentary glaucoma), with inadequate response to prior medical glaucoma therapy (e.g. uncontrolled despite treatment with IOP-lowering medication).

There were, however, cross-trial differences regarding specific baseline IOP levels and medication requirements. The MINIject trials specified IOP levels between 21 mm Hg and 35 mm Hg, with prior usage of between 1 and 4 IOP-lowering medications. In contrast, post-washout IOP level requirements in the iStent trials ranged from 22 mm Hg to 39 mm Hg. Medication limits were not specified in 3 out of 7 iStent trials, while 1 trial only enrolled patients who used a single IOP-lower medication (see Table 7).

Table 7 Eligibility criteria of trials included in ADAR submission

Trial ID (data source)	Glaucoma diagnosis requirements	Baseline IOP requirements	Prior medication requirements
MINIject			
STAR-I	Adults with POAG or SOAG, uncontrolled with ≥1 IOP-lowering medications undergoing a standalone procedure	21 mm Hg < IOP <35 mm Hg in the study eye	Usage of 1–4 different topical hypotensive medication(s)
STAR-II			
STAR-III			
STAR-IV			
iStent			

Trial ID (data source)	Glaucoma diagnosis requirements	Baseline IOP requirements	Prior medication requirements
Voskanyan 2014	Adults with POAG or SOAG (pseudoexfoliative, pigmentary), uncontrolled (IOP \geq 22 mm Hg and <38 mm Hg after washout of medications) with \geq 2 IOP-lowering medications undergoing a standalone procedure Baseline IOP (post washout): 22 mm Hg to 38 mm Hg	Untreated mean IOP \geq 22 mm Hg and <38 mm Hg after washout of medications	Usage of at least 2 medications
Hengerer 2019; Hengerer 2022	Adults with POAG, NAG or secondary glaucoma	History of inadequate response to prior surgical and medical glaucoma therapy	
Lindstrom 2020	Adults with POAG with 1 IOP-lowering medication Baseline IOP (post washout): 22 mm Hg to 38 mm Hg	Medicated IOP at screening of 18 mm Hg to 30 mm Hg. Unmedicated (post washout) IOP of 22 mm Hg to 38 mm Hg	Usage of 1 topical ocular hypotensive medication
Arnlijots 2021	Adult with mild to moderate OAG undergoing a standalone procedure or combined cataract surgery (or goniotomy, this arm not included) Baseline IOP (without washout): 15 mm Hg to 35 mm Hg	Preoperative IOP (without washout) between 15 mm Hg and 35 mm Hg	NR
Pahlitzsch 2021	Adults with POAG which had received iStent (or selective laser trabeculoplasty or trabeculectomy, these arms not included)	NR	NR
Katz 2018	Adults with OAG (POAG, pseudoexfoliative or pigmentary glaucoma) Baseline IOP (post washout): 22 mm Hg to 38 mm Hg	Preoperative IOP 18 mm Hg to 30 mm Hg and unmedicated (post washout) IOP 22 mm Hg to 38 mm Hg	Usage of 1–3 glaucoma medications
Ahmed 2020	Adults with OAG Baseline IOP (post washout): 23 mm Hg to 39 mm Hg	Baseline IOP (post washout): 23 mm Hg to 39 mm Hg	NR

Abbreviations: IOP = intraocular pressure, mm Hg = millimetres of mercury, NAG = Narrow Angle Glaucoma, NR = not reported, OAG = Open-angle glaucoma, POAG, pseudoexfoliative or pigmentary glaucoma), SOAG = secondary open angle glaucoma
Source: Adapted from Appendix B, Table 44-46 of ADAR submission

Comparison of trial baseline characteristics

Baseline characteristics of the identified trials are summarised in Table 8. The applicant concluded broad similarity of the trials, although there were several important differences to note:

- Mean medicated IOP in the 4 STAR studies was above the normal range for adults (12–21 mm Hg), whereas this was only the case for 2 of the 7 iStent studies (Voskanyan 2014 and Hengerer 2019/Hengerer 2022). Differences in baseline IOP levels were likely to introduce ceiling effects, with greater room for IOP improvements in studies with higher average IOP levels and, therefore, a greater likelihood of observing more preferential treatment effects.

- Mean age in the STAR trials ranged from 61 to 69 years, compared to 65 to 76 years in the iStent trials.
- STAR trials were mainly conducted in non-white populations (except for STAR-II), whereas iStent trials were conducted in majority white populations.

Given that unanchored ITCs require there to be no heterogeneity in any effect-modifying or prognostic factors between trials, the imbalances listed above are likely to have compromised the validity of the ITC analysis.

Table 8 Baseline characteristics of trials included in ADAR submission

Trial ID (data source)		n patients (eyes)	Ethnicity, % white	Mean age (years)	% Male	Mean (SD) no. medications	Mean (SD) medicated baseline IOP, mm Hg
MINject							
STAR-I	(Denis 2019 ⁹ ; Denis 2022 ¹⁰)	26	0%	69.4 (11.1)	54%	2.0 (1.1)	23.2 (3.3)
STAR-II	García-Feijóo 2020 ¹¹)	31	81%	69.5 (10.9)	29%	3.0 (1.2)	24.6 (3.7)
STAR-III	(Data on file)	24	0%	66.5 (6.0)	64%	2.2 (0.9)	23.6 (3.1)
STAR-IV	(Data on file)	21	0%	61.3	57%	2.5 (1.1)	24.3 (3.2)
iStent							
1	Voskanyan 2014	99	96%	66.4 (10.9)	43%	2.21 (0.44)	22.1 (3.3)
2	Hengerer 2019; Hengerer 2022	(44)	100%	71.3 (10.5)	52%	2.98 (0.88)	25.3 (6.0)
3	Lindstrom 2020	57	100%	65.3 (9.0)	53%	1 (0)	19.5 (1.5)
4	Arnlijots 2021	14	NR (conducted in Sweden)	72.0 (12.1)	46%	3.0 (1.1)	20.6 (6.4)
5	Pahlitzsch 2021	66	NR (conducted in Germany)	76.0 (8.9)	47%	2.2 (1.2)	19.5 (2.0)
6	Katz 2018	41	NR (conducted in US, Italy, Germany, Spain)	NR	NR	1.76 (NR)	20.1 (1.6)
7	Ahmed 2020	77	64% European	66.5 (9.5)	42%	2.7 (0.8)	19.1 (3.6)

Abbreviations: IOP = intraocular pressure, mm Hg = millimetres of mercury, NR = not reported, SD = standard deviation

Source: Table 10 of ADAR submission

9 Denis P, Hirneiß C, Reddy KP, et al. A First-in-Human Study of the Efficacy and Safety of MINject in Patients with Medically Uncontrolled Open-Angle Glaucoma (STAR-I). *Ophthalmol Glaucoma* 2019;2(5):290-97.

10 Denis P, Hirneiß C, Durr GM, et al. Two-year outcomes of the MINject drainage system for uncontrolled glaucoma from the STAR-I first-in-human trial. *Br J Ophthalmol* 2022;106(1):65-70.

11 García Feijóo J, Denis P, Hirneiß C, et al. A European Study of the Performance and Safety of MINject in Patients With Medically Uncontrolled Open-angle Glaucoma (STAR-II). *J Glaucoma* 2020;29(10):864-71.

11. Comparative safety

Adverse events (AEs) for MINject were infrequent and generally not serious. Anterior chamber inflammation was the most reported AE (mainly associated with surgery). Visual acuity reductions were reported by 17% of patients, and 11% reported hyphaema. Other AEs, such as conjunctival haemorrhage, vision blurring, and cataract progression, occurred in less than 10% of patients. The assessment group queries whether the data presented are a comprehensive picture of the safety profile for MINject, given there is no mention of serious AEs that are commonly associated with stent implantation (i.e. IOP elevation, stent blockage or obstruction, stent malposition, and hypotony). Furthermore, the assessment group note a lack of long-term safety data, with current evidence based on 24 months of follow-up. This is particularly concerning in the context of the removal of the Cypass device at the 5-year mark due to safety concerns.

Similarly low numbers of AEs were reported across the iStent trials, with most occurring in less than 10% of patients. Notably, in a trial of 41 patients (Katz 2018), loss in best-corrected visual acuity (BCVA) ≥ 1 line occurred at a rate of 21.1%, and cataract surgery at a rate of 13.2%. In a further clinical trial with 14 patients, 6 eyes needed additional glaucoma treatment due to inadequate IOP control (~43%) (Arnijots 2021).

A comparison of adverse event rates for MINject and iStent is presented in Table 9. Overall, there were insufficient data to draw any meaningful conclusion regarding the relative safety of MINject and iStent. Furthermore, data presented comparing the AE rates of the 2 devices (as shown in Table 9) were considered potentially misleading, given the applicant used hyphens to represent both missing data and instances where events did not occur in $n > 2$ patients.

Table 9 Adverse events comparison (reported as number (%) of patients in >2 patients in each study)

AE	MINject	iStent							
	Pooled (STAR-I to STAR-IV)	Pooled	Voskanyan 2014	Hengerer 2019; Hengerer 2022	Lindstrom 2020	Arnlijots 2021	Pahlitzsch 2021	Katz 2018	Ahmed 2020
N	102	398	99	44	57	14	66	41	77
Anterior chamber inflammation	31 (30)	-	-	-	-	-	-	-	-
Visual acuity reduced	17 (17)	-	-	-	-	-	-	-	-
Hyphaema	11 (11)	-	-	-	-	-	-	-	-
Conjunctival haemorrhage	5 (5)	-	-	-	-	-	-	-	-
Vision blurred	8 (8)	-	-	-	-	-	-	-	-
Pupillary deformity	8 (8)	-	-	-	-	-	-	-	-
Cataract/ progression	3 (3)	15 (4)	-	-	2 (4)	4 (7)	-	5 (12)	4 (5)
Device not visible*	-	13 (3)	13 (13)	-	-	-	-	-	-
Device obstruction	-	13 (3)	3 (3)	-	-	-	-	-	10 (13)
Posterior capsular opacification	-	2 (0)	2 (2)	-	-	-	-	-	-
BCVA >1 to 2 lines	-	11 (3)	-	-	3 (5) (>1 line)	-	-	8/38 (21) (≥1 line)	-
VF defect	-	4 (1)	-	4 ** (9)	-	-	-	-	-
Additional glaucoma procedure	-	18 (5)	-	2 (5)	-	6 (43)	5	3 (7)	2 (3)
Corneal oedema (transient)	-	2(0)	-	-	-	2 (14)	-	-	-

Abbreviations: AE = adverse event, BCVA = best-corrected visual acuity, BL = baseline, IOP = intraocular pressure, SAE = serious adverse events, VF= visual field

Source: Based on Table 21 of ADAR submission, with correction of data for Katz 2018 included in the ADAR.

* Upon gonioscopy

** Corrected Distance Visual Acuity (CDVA) of worse than 20/50

Hyphens indicate that data were not reported (or did not occur in n>2 patients in that study)

12. Comparative effectiveness

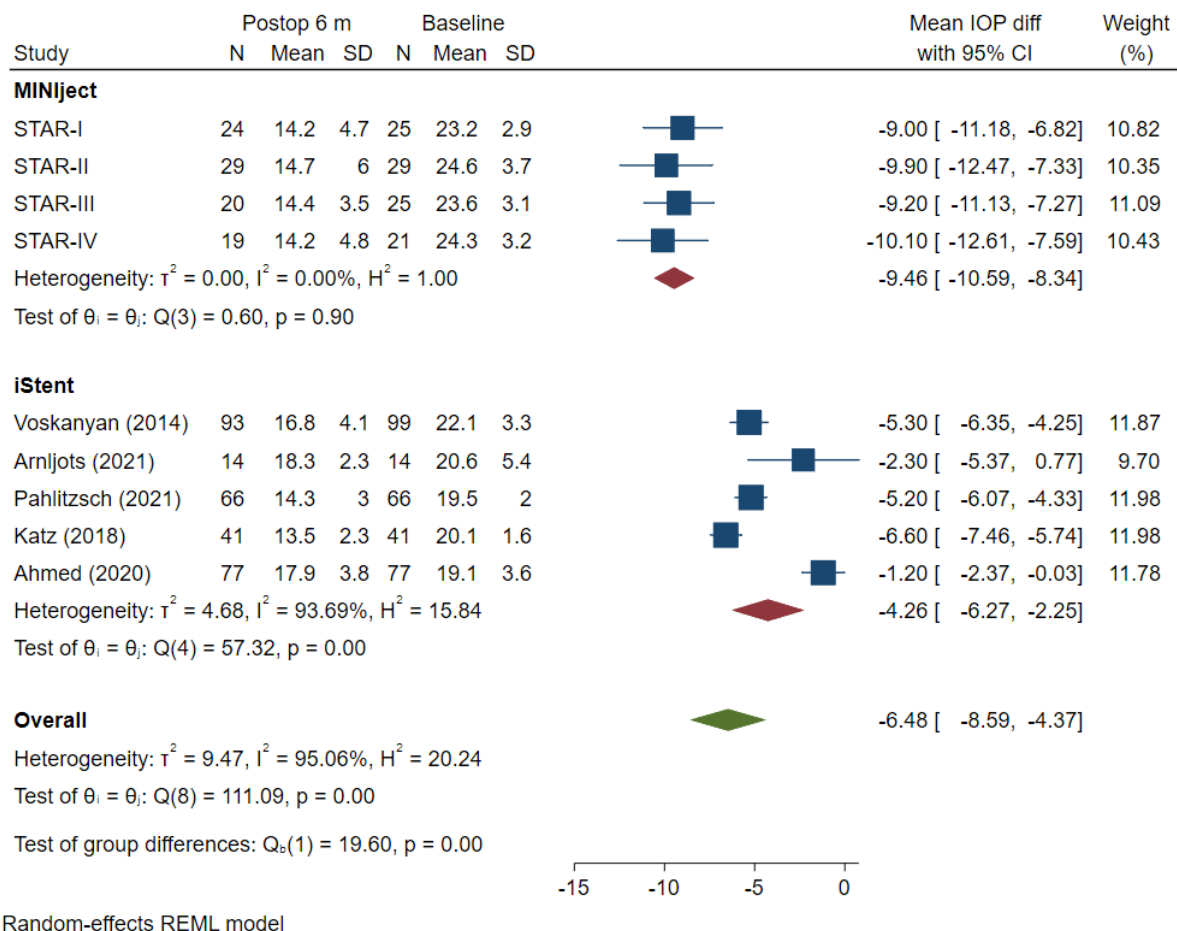
Meta-analysis results: Change from baseline in mean IOP (mm Hg)

Based on the meta-analysis of estimates from the STAR trials, MINject was found to be associated with a -9.46 mm Hg reduction (95% confidence interval (CI): -10.59, -8.34) in IOP at 6 months (Figure 1), -8.38 (95% CI: -9.51, -7.24) at 12 months, and -9.57 (95% CIL -10.73, -8.41) at 24 months. Between-study heterogeneity was minimal, as measured by the I^2 statistic, with zero values reported across all time points.

For iStent, meta-analysed IOP change from baseline estimates was -4.26 mm Hg (95% CI: -6.27, -2.25) at 6 months, -5.39 (95% CI: -8.02, -2.76) at 12 months, and -4.92 (95% CI -8.86, -0.98) at 24 months, indicating less preferential treatment outcomes relative to MINject. Statistical heterogeneity was high across the iStent trials, with $I^2 > 90\%$ at each time point.

The applicant claimed that the lower inter-study variability in mean IOP reduction observed for MINject versus iStent was indicative of more reliable treatment efficacy. While the assessment group acknowledges the high degree of consistency in the performance of the MINject, particularly in the context of demographic differences across the STAR trials (STAR-I, -II, -IV [Latin American and Indian] and STAR-II [European]), it is important to note that the MINject trials were identically designed, with consistent eligibility criteria. As a result, patient populations of the STAR trials are likely to be homogenous and thus treatment outcomes more consistent. In contrast, the iStent trials varied in design, with differences in patient eligibility criteria and baseline characteristics. As such, a higher degree of statistical heterogeneity was anticipated.

Figure 1 Mean change from baseline in intraocular pressure at 6 months (mmHg)



Random-effects REML model

Abbreviation: CI = confidence interval; SD = standard deviation; IOP = intraocular pressure

Source: Figure 3 of ADAR submission

'Test of group differences' p value provides the meta-regression p value for the indirect treatment comparison analyses presented in Table 15 of the ADAR submission (reproduced in Table 11)

To better understand the heterogeneity observed between the iStent trials, the assessment group performed a correlation analysis, evaluating the relationship between baseline IOP levels and mean IOP differences at 6, 12 and 24 months (see Table 10). Negative correlations were observed, indicating that studies with higher baseline IOP levels were associated with greater mean IOP reductions (Pearson's correlation coefficient [ρ] = -0.35 at 6 months, ρ = -0.77 at 12 months, and ρ = -0.96 at 24 months). The assessment group acknowledged this analysis was limited due to small sample size, nevertheless, the outcomes supported a possible ceiling effect, whereby stronger treatment effects are observed in studies with higher baseline IOP levels because there is greater possibility for improvement.

An additional correlation analysis was performed, incorporating values for baseline IOP and mean IOP differences for the MINIject studies. Here, stronger negative correlations were observed than before (ρ = -0.87 at 6 months, -0.85 at 12 months, and -0.95 at 24 months). These findings suggested that higher IOP reductions observed for the MINIject studies versus iStent studies may be attributable at least in part to cross-trial differences in baseline IOP levels, as opposed to poorer performance of the iStent device.

Table 10 Relationship between baseline intraocular pressure and mean intraocular pressure difference for MINject and iStent trials

Study	Baseline IOP	Mean IOP difference		
		6 months	12 months	24 months
MINject				
STAR-I	23.2	-9.0	-7.20	-9.40
STAR-II	24.6	-9.9	-9.50	-9.10
STAR-III	23.6	-9.2	-8.00	-10.00
STAR-IV	24.3	-10.1	-9.00	NR
iStent				
Voskanyan 2014	22.1	-5.30	-6.40	NR
Hengerer 2019; Hengerer 2022	25.3	NR	-10.10	-10.30
Arnljots 2021	20.6	-2.30	-2.20	-4.60
Pahlitzsch 2021	19.5	-5.20	-5.00	-4.00
Katz 2018	20.1	-6.60	-7.30	NR
Ahmed 2020	19.1	-1.20	-1.00	-1.00
Correlation analysis (baseline IOP vs mean IOP difference) *				
iStent studies only	-	-0.35	-0.77	-0.96
All studies	-	-0.87	-0.85	-0.95

Abbreviation: IOP = intraocular pressure

Source: adapted from values presented in Figures 3-5 of ADAR

*Values presented are Pearson's correlation coefficients.

The applicant further suggested that lower IOP reductions observed in the iStent trials may be reflective of insertion location, stating that devices inserted into Schlemm's canal are constrained by episcleral venous pressure, which limits the extent to which trabecular meshwork bypass devices can achieve low IOPs; however, contradictory data were presented in the ADAR, showing similarly high proportions of patients achieving IOP normalisation (≤ 18 mm Hg) in both the MINject and iStent trials.

ITC results: Change from baseline in mean IOP (mm Hg)

The ITC analysis for change from baseline in mean IOP demonstrated statistically significant superiority of MINject over iStent at 6, 12, and 24 months (Table 11). More specifically, MINject was shown to reduce IOP by an additional 5.20 mm Hg (95% CI 2.62, 7.78; $p=0.00$) at 6 months, 3.01 mm Hg (95% CI: -0.47, 6.48; $p=0.04$) at 12 months and 4.63 mm Hg (95% CI: -0.07, 9.33; $p=0.03$) at 24 months.

Table 11 Primary outcome indirect treatment comparison results: Mean change from baseline in intraocular pressure

Timepoint (post procedure)	Mean treatment difference, mm Hg (95% CIs): (MINject – iStent)	p value for difference (meta-regression)
6 months	-5.20 (-7.78, -2.62)	0.00
12 months	-3.01 (-6.48, 0.47)	0.04
24 months	-4.63 (-9.33, 0.07)	0.03

Abbreviations: CI = confidence interval; IOP = intraocular pressure

Source: Table 15 of ADAR submission

The mean difference and 95% CI are calculated as a mean difference using t-test. The p value is calculated from the meta-analyses using meta-regression. Meta-analyses were conducted from data sourced from the STAR-I to -IV study data and from the iStent study publications cited as Trial IDs.

While the assessment group acknowledged the consistency of the treatment benefit presented for MINject versus the iStent device, the outcomes of the ITC analysis were fundamentally biased, given the relationship between baseline IOP levels and mean IOP differences at 6, 12 and 24 months (Table 10). Population-adjusted methods (e.g. a matching adjusted ITC) would provide a more robust estimation of the relative effects of MINject and iStent; however, in place of a population-adjusted ITC, a more conservative estimate of relative effectiveness can be computed by restricting the analyses to include iStent studies with similar baseline IOP levels to the STAR studies (e.g. those with baseline IOP levels greater than the normal range [12–21 mm Hg]: Hengerer [2019] and Voskanyan [2014]).

Table 12 provides estimates based on an alternative ITC analysis conducted by the commentary comparing the efficacy of MINject and iStent using only studies with similar IOP at baseline. At 6 months, MINject was associated with a statistically significant improvement in IOP versus iStent, with a mean treatment difference of -4.16 mm Hg (95% CI: -5.17, -2.61; p=0.00). No significant differences were observed between MINject and iStent at 12 and 24 months.

Table 12 Re-estimated primary outcome indirect treatment comparison results: Mean change from baseline in intraocular pressure

Timepoint (post procedure)	Mean IOP difference (SD) MINject	Mean IOP difference (SD) iStent*	Mean treatment difference, mm Hg (95% CIs): (MINject – iStent)**	p value (2-sided)
6 months	-9.46 (0.58)	-5.30 (0.54)	-4.16 (-5.71, -2.61)	0.00
12 months	-8.36 (0.58)	-8.13 (1.84)	-0.23 (-4.01, 3.55)	0.91
24 months	-9.57 (0.59)	-10.30 (1.08)	0.73 (-1.68, 3.14)	0.55

Abbreviations: IOP = intraocular pressure, SD = standard deviation, CI = confidence interval

Source: Compiled for the commentary

*Mean IOP differences for iStent were computed by meta-analysing results of the Voskanyan and Hengerer trials where available.

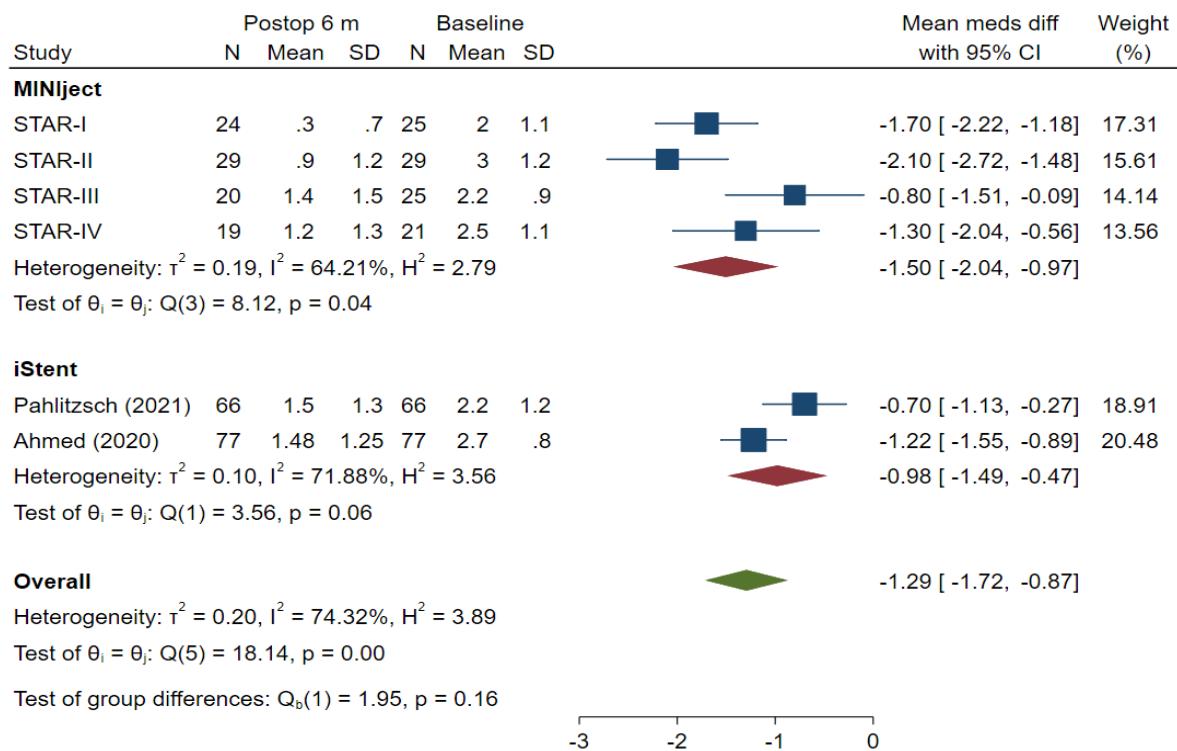
**Mean treatment differences between MINject and iStent were calculated using the Bucher method (simple subtraction). 95% confidence intervals were constructed based on combined variance estimates of the two treatments.

Meta-analysis results: Mean change from baseline in the number of IOP-lowering medications

Meta-analysed estimates for mean change from baseline in the number of IOP-lowering medications for MINject were -1.50 (95% CI: -2.04, -0.97) at 6 months (Figure 2), -1.27 (95% CI: -1.73, -0.82) at 12 months and -1.0 (95% CI -1.67, -0.32) at 24 months. Between-study heterogeneity varied across the different time intervals, with the I² value ranging from 48% to 64%.

Smaller reductions in medication usage were observed for iStent, with meta-analysed treatment effects of -0.98 (95% CI -1.49, -0.47) at 6 months, -0.96 (95% CI -1.23, -0.69) at 12 months and -0.56 (95% CI -0.89, -0.23) at 24 months. Statistical heterogeneity was apparent between the iStent trials, with I² values of 72% and 35% at 6 and 24 months, respectively.

Figure 2 Mean change from baseline to month 6 in number of intraocular pressure-lowering medications



Random-effects REML model

Abbreviations: CI = confidence interval; SD = standard deviation

Source: Figure 6 of ADAR submission

The mean difference and 95% CI are calculated as a mean difference using t-test. The p value is calculated from the meta-analyses using meta-regression.

ITC results: Mean change from baseline in the number of IOP-lowering medications

The ITC analysis for change from baseline in the number of IOP-lowering medications demonstrated broad equivalence of MINIject and iStent (Table 13). Nominal differences were observed, slightly favouring MINIject; however, these results were not statistically significant.

Although baseline IOP-lowering medication usage was comparable across the MINIject and iStent trials, the assessment group maintained that a population-adjusted approach would produce more robust results, given imbalances in other baseline characteristics.

Table 13 Indirect treatment comparison key outcome results: Impact on intraocular pressure-lowering medication use

Endpoint	Timepoint (post procedure)	Mean treatment difference (95% CIs) (MINIject – iStent)	p value for difference (meta-regression)
Change from baseline in the mean number of medications, n	6 months	-0.54 (-1.32, 0.25)	0.16
	12 months	-0.33 (-0.79, 0.12)	0.25
	24 months	-0.48 (-1.21, 0.25)	0.26

Abbreviations: CI = confidence interval, IOP = intraocular pressure

Source: Table 16 of ADAR submission

The mean difference and 95% CI were calculated as a mean difference using t-test. The p value was calculated from the meta-analyses using meta-regression.

Summary of clinical claim

The applicant claimed use of MINject results in superior effectiveness and noninferior safety compared with iStent. Based on the evidence presented in the ADAR submission, the assessment group do not feel that this claim has been adequately defended. Concerns were raised regarding the validity of the comparative effectiveness analyses and further the lack of data presented to draw any informative conclusions regarding the comparative safety of the proposed technology compared to iStent in the proposed population.

Applicability to the Australian setting

There remained a high degree of uncertainty regarding the external validity of the clinical trials included in this submission. Specifically, whether the clinical trial populations of glaucoma patients who have failed or are contraindicated to conventional therapies including IOP-lowering medications, and assessed as suitable for MBGS, align with and are reflective of glaucoma patients seen in clinical practice in Australia.

Furthermore, the pivotal trials used to demonstrate the efficacy and safety of MINject in the ADAR submission were conducted mainly in Latin American and Indian populations. The generalisability of the results of these trials to the Australian population remains uncertain, with no evidence presented by the applicant to compare the demographic characteristics of patients in the analysis to those in the Australian and New Zealand Registry of Advanced Glaucoma,¹² or to consult clinical experts who would confirm the generalisability of the MINject trials to clinical practice in Australia.

13. Economic evaluation

The ADAR presented a cost-minimisation approach to support the applicant's position for an equivalent MBS fee of \$329.40 (Item 42504) for MINject in line with the comparator product, iStent. The key modelling components are summarised in Table 14.

¹² Australian & New Zealand Registry of Advanced Glaucoma. Available: <https://anzrag.com.au/>

Table 14 Summary of the economic evaluation

Component	Description
Perspective	Health system perspective
Population	Patients with glaucoma requiring implantation of a MBGS stent system into the suprachoroidal space, if: (a) conservative therapies have failed, are likely to fail or are contraindicated; and (b) the service is performed by a specialist with training that is recognised by the Conjoint Committee for the Recognition of Training in Micro-Bypass Glaucoma Surgery
Prior testing	None
Comparator	iStent (Glaukos) MBGS stent system (inserted via the trabecular meshwork)
Type of analysis	Cost-minimisation analysis
Outcomes	Comparative clinical evidence demonstrated that use of MINject rather than the comparator iStent resulted in greater IOP reductions post-surgery and reduced requirement for IOP-lowering medication. Based on the evidence presented, safety was assumed to be noninferior
Time horizon	Not applicable as the economic evaluation did not use a model-based approach. The cost-minimisation analysis was undertaken where only the proposed MBS item was included.
Computational method	
Generation of the base case	
Health status	
Cycle length	
Transition probabilities	
Software	

Abbreviations: IOP = intraocular pressure; OVD = Ophthalmic viscoelastic device; MBGS = micro-bypass glaucoma surgery
Source: Based on Table 22 of the ADAR submission

In the primary analysis, the applicant provided evidence supporting the comparability of the surgical procedures for the MINject and iStent MBGS (Table 15).

Table 15 Detail of MINject and iStent standalone procedure steps

Step	MINject®	iStent Inject®
Pre-procedure	Anaesthesia for the eye	Anaesthesia for the eye
Eye preparation	Antiseptic applied to eye	Antiseptic applied to eye
	Eye opened with eyelid speculum	Eye opened with eyelid speculum
	Head rotated, microscope rotated and positioned above the eye	Head rotated, microscope rotated and positioned above the eye
Procedure	Incision made to cornea with 2.0–2.2 mm knife	Incision made to cornea with 2.0 mm knife
	Ophthalmic viscoelastic device (OVD) inserted into anterior chamber and on top of cornea	Ophthalmic viscoelastic device (OVD) inserted into anterior chamber and on top of cornea
	Gonioprism used to view the angle	Gonioprism used to view the angle
	MINject device inserted through the incision and viewed under the gonioprism as it approaches the angle	iStent Inject device inserted through the incision and viewed under the gonioprism as it approaches the angle
	MINject device sheath inserted into the supraciliary space into desired implantation location	Slide retraction button to draw back insertion sleeve and advance trocar tip to the centre of the trabecular meshwork at implantation location

Step	MINIject®	iStent Inject®
	Wheel of MINIject device rolled back slowly to withdraw the sheath to lay the implant in place	Press trigger to inject stent through trabecular meshwork and into Schlemm's Canal; repeat for second stent
	MINIject device removed from the eye	iStent injector removed from the eye
	Irrigation and aspiration performed to flush out OVD from the eye	Irrigation and aspiration performed to flush out OVD from the eye
	Incision hydrated	Incision hydrated
	Eyelid speculum removed	Eyelid speculum removed
	Anti-inflammatory and steroidal drops applied	Anti-inflammatory and steroidal drops applied
	Eye patch applied	Eye patch applied
Post procedure	Anti-inflammatory and steroidal drops prescribed to patient for several weeks	Anti-inflammatory and steroidal drops prescribed to patient for several weeks
	All glaucoma medication stopped	All glaucoma medication stopped

Abbreviations: OVD = Ophthalmic viscoelastic device

Source: Table 23 of ADAR submission

Green colouring represents similarities, yellow represents differences

According to Section 3 of the MSAC Guidelines, a cost-minimisation approach should only be used when the proposed service has been demonstrated to be noninferior to its main comparator(s) in terms of both effectiveness and safety. As noted above, the assessment group considered there to be material uncertainty associated with the relative safety of MINIject compared with iStent (comparator).

While the assessment group agrees that a cost-minimisation approach may be reasonable given the similarity in the delivery and implementation of the two devices (see Table 15), further analysis of the relative safety of MINIject compared with iStent is required to ensure that the assumption of noninferiority, with respect to both effectiveness and safety, is met. Furthermore, the applicant has provided little to no discussion on the cost of managing AEs, or the reduced health-related quality of life associated with these. Understanding these impacts may aid in the quantification of the uncertainty associated with the comparative safety profile of MINIject.

While the assessment group accepted the conclusions of the applicant regarding the comparability of the surgical procedures for the MINIject and iStent MBGS device, the assessment group could not conclude with confidence that an equivalent MBS fee of \$329.40 (consistent with MBS item 42504) was justified given the uncertainty of the comparative safety profile of MINIject.

In the secondary analysis, the applicant has estimated an additional cost saving of \$585.84 per patient in the first 2 years after standalone MBGS, as a result of reductions in IOP-lowering medication and ocular surface disease (OSD) treatment costs of MINIject versus iStent. This cost saving comprised a reduction of \$345.26 resulting from a mean change in the number of IOP-lowering medications of -0.48 (95% CI -1.21, 0.25) at 24 months, and a further \$240.58 from reduced OSD treatment costs (Table 16 and Table 17).

Table 16 Cost savings associated with reductions in intraocular pressure-lowering medication as presented in ADAR submission

Step	Input	Value	Source
a	Lumigan DPMQ (Sep 23)	\$29.56	Lumigan PF PBS DPMQ (Sep 23)
b	Annual cost	\$349.31	365 days/30 unit doses
c	Additional mean-IOP lowering medication reduction over comparator	0.48	Meta-analysis result at 24 months From ITC (incremental mean reduction in number of IOP-lowering medications at 24 months)
d	Annual cost saving	\$172.63	(b x c)
d	Expected cost saving per MINInject MBGS procedure (per patient over 2 years)	\$345.26	(d x 2)

Abbreviations: DPMQ = Dispensed Price for Maximum Quantity, IOP = intraocular pressure, ITC = indirect treatment comparison, MBGS = Micro-Bypass Glaucoma Surgery, OVD = Ophthalmic viscoelastic device, PBS = Pharmaceutical Benefits Scheme, PF = Preservative free
Source: Table 26 of ADAR submission

Table 17 Cost savings associated with reductions in ocular surface disease treatment costs as presented in ADAR submission

Step	Input	Value	Source
a	Prevalence of significant OSD in Australian glaucoma patients	39%	Chan 2013 ¹³
b	Additional reduction of IOP-lowering medication over comparator (MINInject vs. iStent)	0.48	Meta-analysis result at 24 months From ITC (incremental mean reduction in number of IOP-lowering medications at 24 months)
c	Reduction factor	50%	Conservative reduction of 50% impact on costs factored in, since the magnitude of the relationship between reduction in glaucoma medication use and reduction in OSD is not established. See supportive data from Denis 2022 below table.
d	OSD direct health care annual cost (2012)	\$1,061.25	Chan 2013 (2012 costs)
e	OSD direct health care annual cost (2022-23)	\$1,285.16	Chan 2013 Inflated using health inflator from 2012-13 to 2022-23 AIHW - health inflator index . ^a
Total	Expected cost savings per MINInject MBGS procedure (per patient, over 2 years)	\$240.58	(a x b x c x e x 2)

Abbreviations: AIHW = Australian Institute of Health and Welfare, IOP = intraocular pressure, ITC = indirect treatment comparison, MBGS = Micro-Bypass Glaucoma Surgery, OSD = ocular surface disease

Source: Table 27 of ADAR submission

^a For 2021-22 and 2022-23 health inflation reported in 2020-21 of 1.96 is also assumed.

Insufficient detail regarding the management of OAG with IOP-lowering medication was provided by the applicant, with particular reference to the use of medication in the target population: patients for whom conservative therapies have failed, are likely to fail, or are contraindicated.

13 Chan, C.C., Crowston, J.G., Tan, R., et al. (2013). "Burden of Ocular Surface Disease in Patients With Glaucoma From Australia." *Asia Pac J Ophthalmol (Phila)* 2(2): 79-87.

The assessment group accepted that there may be some cost offsets associated with reductions in IOP-lowering medication but considered the savings estimated by the applicant to be uncertain and likely an overestimate of the true savings. Furthermore, the assessment group did not consider there to be sufficiently robust evidence to suggest an incremental saving from a reduction in OSD treatment associated with MINject compared with iStent. As stated by the applicant, the relationship between reduction in glaucoma medication use and reduction in OSD is not established. Additionally, as noted previously, the data on quality of life as collected in STAR-1 were based on a small sample size, and the results (presented in Table 20 of the ADAR submission) were potentially misleading.

14. Financial/budgetary impacts

The applicant adopted a market-share approach to estimate financial implications, based on MBS statistics for the use of standalone procedure 42504, which covers insertion of the comparator iStent. The anticipated uptake of MBS using MINject is **Redacted%** of the current MBS item 42504 procedures in Year 1 (2024/25), increasing gradually by **Redacted%** per year, see Table 18. The estimate assumed a gradual uptake as more surgeons are trained to insert MINject and are convinced of its positive outcomes, with this growth constrained by the iSTAR resources available to undertake training, as well as the preference of many surgeons to continue to use the comparator iStent.

Table 18 Proposed uptake of MINject as presented in ADAR submission

Item 42504 services in 2022/23:	Services by MBS item (financial year)						
	2022/23	2023/24	2024/25	2025/26	2026/27	2027/28	2028/29
390							
Assumed market growth (%)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Market size	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
% replacement of existing item 42504	-	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Estimated MINject services	-	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted

Abbreviations: MBS = Medicare Benefits Schedule

Source: Table 31 of ADAR submission

The assessment group considered the evidence provided on the prevalence and market uptake of MINject to be clear and reasonable. Under the current assumption that the proposed MBS fee be equal to the comparator, and excluding uncertain scenarios that could potentially incur a greater net cost to the MBS (see Population), the assessment group agreed that there would be no net financial impact to the MBS, see Table 19.

Table 19 Net financial implications of MINject as presented in ADAR submission

Parameter	Financial year					
	2023/24	2024/25	2025/26	2026/27	2027/28	2028/29
Estimated use and cost of the proposed health technology (standalone MBGS using MINject)						
Number of services of MINject standalone item	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Cost per service (85% benefit level)	\$280.00	\$280.00	\$280.00	\$280.00	\$280.00	\$280.00
Cost to the MBS	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Reductions in use and cost of current item 42504 (standalone MBGS using iStent)						
Reduction in use of current item 42504 (using comparator iStent)	Redacted	Redacted	Redacted	Redacted	Redacted	Redacted
Cost per service (85% benefit level)	\$280.00	\$280.00	\$280.00	\$280.00	\$280.00	\$280.00
Net change in costs to the MBS	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
Net financial impact to the MBS	\$0	\$0	\$0	\$0	\$0	\$0

Abbreviations: MBS = Medicare Benefits Schedule, MBGS = Micro-Bypass Glaucoma Surgery
Source: Table 33 of ADAR submission

15. Other relevant information

Equality considerations

The procedure can only be performed by trained and specialised ophthalmologists who are usually based in major city centres. This may disadvantage patients from rural communities.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The evidence provided did not adequately address the issue of longer-term safety of the MINject device.
- There are currently no specific data from the manufacturer or the community to be able to determine the nature of clinical need and clinical place for this device, and it is unclear whether it would be used in some patients who would not use the iStent.
- The safety profile of the intervention and the comparator were similar. There were insufficient data to draw any meaningful conclusion regarding the relative safety, although there was no reason to believe there was a current safety risk.
- While the clinical data showed a trend towards improved clinical effectiveness, a more justifiable position based on the available evidence would be to assume noninferiority in reducing IOP levels.

Economic issues:

- The ADAR presented a cost-minimisation analysis. A clinical claim of superiority ideally warrants a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA), however the cost-minimisation approach (CMA) may potentially be acceptable given the applicant is not seeking a price premium, and the clinical evidence may better support non-inferior than superior effectiveness.
- There are sufficient data and existing models that could have been used for a more informative economic analysis.
- It is not clear whether the equivalent cost was justifiable given the uncertainty surrounding the comparative safety profile of MINject.

Financial issues:

- The claimed cost-offsets from reduced ocular surface disease (OSD) medication with MINject compared to the iStent were highly uncertain as they were not supported by evidence that OSD medication was reduced.
- There may be a small risk of leakage (increased utilisation and cost), because the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) suggested that there is a small cohort who would be specifically targeted for this stent. No data are available to quantify the likely risk.

ESC discussion

ESC noted that this was an application from iSTAR Medical requesting Medicare Benefits Schedule (MBS) funding for micro-bypass glaucoma surgery (MBGS) to implant a device such as the MINject into the suprachoroidal space, as a standalone procedure in patients with open angle glaucoma, for whom conservative therapies have failed, are likely to fail or are contraindicated.

ESC noted glaucoma is the most common cause of preventable irreversible blindness in Australia and the rest of the world, due to increased intraocular pressure (IOP). Therapy is based on different methods of lowering IOP, which in Australia currently include conservative management (eyedrops: topically delivered medication), laser trabeculoplasty, MBGS, and conventional surgery.

ESC noted previous *Application 1541 – Micro-bypass glaucoma surgery device implantation in trabecular meshwork or suprachoroidal space as a standalone procedure in patients with open angle glaucoma* was considered by MSAC in November 2018 and August 2019¹⁴. ESC noted application 1541 had not been supported by MSAC in November 2018 for the following reasons: unclear eligibility criteria and high leakage risk to other populations, poor comparative safety data, poor comparative efficacy and unsatisfactory economic assessment. A resubmission of application 1541 was later supported by MSAC in August 2019, resulting in the MBS listing of trabecular MBGS as a standalone procedure (now MBS item 42504) – however the re-application excluded suprachoroidal minimally invasive glaucoma surgery (MIGS)/MBGS due to the withdrawal at the time of the suprachoroidal MIGS CyPass stent from the Australian market due to safety concerns.

¹⁴ MSAC application 1541 – Micro-bypass glaucoma surgery (MBGS) device implantation as a standalone procedure in patients with open-angle glaucoma (OAG). Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1541-public>

ESC noted that insertion of a stent into the suprachoroidal space is already publicly funded under MBS item 42705, for insertion in association with cataract surgery (and removal if required, using MBS item 42505). The device is therefore already on the Prescribed List (PL).

ESC noted that the MINject® and MINject® S (next-generation device) are included on the Australian Register of Therapeutic Goods (ARTG; both with ARTG ID 400268), and work by enhancing physiological outflow through the uveoscleral pathway. The implants for both devices are identical, as are the procedures – the difference is only in the sheath of the delivery tool. ESC considered the proposed item descriptor would apply to both MINject® and the MINject® S.

ESC noted that the proposed funding arrangement is to extend existing MBS item 42504 to include implantation of the MBGS device into the suprachoroidal space. The proposed fee was the same as the existing MBS item 42504 fee, given the similar cost associated with the insertion of MINject compared with the comparator during MBGS standalone surgery. ESC considered this was reasonable.

ESC noted that within the suprachoroidal space MINject targets the supraciliary space specifically, and is the only device on the market to do so. ESC recalled MSAC’s previous concerns with the suprachoroidal CyPass stent, but noted clinical expert input from RANZCO that as a supraciliary stent targeting the uveoscleral pathway, the MINject had a safety advantage over devices that target the subconjunctival space that create a filtering bleb. ESC considered the safety implications for a supraciliary stent would not necessarily be the same as for suprachoroidal stents in general, and agreed with RANZCO that the MINject would be more appropriately described as a supraciliary stent, and so proposed clarifying the terminology in the item descriptor from “suprachoroidal” to “supraciliary” (Table 20).

ESC noted the item descriptor for MBS item 42504 included the requirement that the specialist performing the service is “recognised by the Conjoint Committee for the Recognition of Training in Micro-Bypass Glaucoma Surgery”, however the Department advised that this committee was never established. ESC noted that RANZCO had recently advised the Department that MBGS training now forms part of the RANZCO training program for all fellows, and the Department proposed removing reference to the Committee from MBS item 42504 (and associated items and explanatory notes). ESC considered this was reasonable, and proposed the qualification requirement be removed.

Table 20 ESC’s updated MBS item descriptor

Category 3 – Therapeutic procedures	
MBS item 42504	
Glaucoma, implantation of a micro-bypass surgery stent system into the <u>suprachoroidal supraciliary space</u> or trabecular meshwork, if:	
(a) conservative therapies have failed, are likely to fail, or are contraindicated; and	
(b) the service is performed by a specialist with training that is recognised by the Conjoint Committee for the Recognition of Training in Micro-Bypass Glaucoma Surgery	
Fee: \$331.05	75% benefit: \$248.30 85% benefit: \$281.40

ESC’s changes to the proposed MBS item descriptor are shown in green font.

ESC noted that no ratified PICO confirmation was available for this application as it followed the expedited MSAC pathway, bypassing PASC – and the applicant had therefore developed its own PICO as described in the ADAR.

ESC noted and welcomed consultation input from 3 professional organisations, and 4 individuals, of whom all were medical specialists. ESC noted consumer concerns with this application included accessibility, as only a small number of clinicians in major city centres can perform this

procedure, and the First Nations population has high levels of glaucoma. ESC noted one surgeon said that the procedure is minimally invasive and avoids medication side effects and extensive surgery.

ESC noted that the comparator selected by the applicant was iStent® (Glaukos), an alternative MBGS stent system implanted via the trabecular meshwork. The applicant reasoned that the iStent device, used within the same MBS item number (42504), was a more appropriate comparator to MINject than other procedures such as selective laser trabeculoplasty and trabeculectomy, because the iStent belongs to the same MBGS class as MINject and has a similar class level of safety and efficacy. The applicant also stated that iStent currently represents the most-used MBGS device in Australia, however details regarding the applicant's clinical expert survey's design and findings were not provided, and the MBS item is brand-agnostic so the insertion of other brands of stent can also be claimed under the existing item. Overall ESC considered there remained some uncertainty as to whether iStent alone was the appropriate comparator. ESC considered the exclusion of any additional relevant comparators may have reduced the amount of direct evidence available to comprehensively assess the intervention.

ESC noted the clinical claim was that MINject has noninferior safety and superior effectiveness compared with iStent.

ESC noted that because there were no head-to-head trials between the MINject and iStent delivery systems, the ADAR used a naïve unanchored indirect treatment comparison (ITC) to estimate the relative effectiveness of the technologies. ESC considered that typically, naïve comparisons are associated with a high degree of uncertainty and there is a high potential for the comparison to be influenced by factors other than the treatments being compared. ESC considered no evidence was provided to mitigate these concerns.

ESC noted that four MINject and seven iStent studies were identified. The MINject trials consisted of four identically designed, prospective, single-arm trials (named STAR-I to STAR-IV), each enrolling between 21 and 31 patients. In contrast, the iStent trials were a collection of single-arm trials and a single case series study, enrolling between 10 and 100 patients. All trials monitored and reported the key efficacy outcomes as well as safety outcomes. ESC considered the iStent trials had more diverse patients, including with respect to ethnicity, and varied in design, which made the comparison more difficult.

ESC noted that there remained a high degree of uncertainty regarding the external validity of the clinical trials included in the ADAR. Specifically, whether the clinical trials populations of glaucoma patients who have failed or are contraindicated to conventional therapies, including IOP-lowering medications, and assessed as suitable for MBGS, align with and are reflective of glaucoma patients seen in clinical practice in Australia. ESC considered the applicability of the evidence was reduced due to the differences in ethnicity, as patients of some ancestry are known to be at increased risk of glaucoma due to thinner cornea and larger optic nerve (African and Hispanic ancestry) or angle and anatomy (Asian ancestry).

Furthermore, ESC noted that the pivotal trials used to demonstrate the efficacy and safety of MINject in the ADAR were conducted mainly in Latin American and Indian populations. ESC considered the generalisability of the results of these trials to the Australian population remained uncertain, with no evidence presented by the applicant to compare the demographic characteristics of patients in the analysis to those in the Australian and New Zealand Registry of Advanced Glaucoma or to clarify with clinical experts their view on the generalisability of the MINject trials to clinical practice in Australia.

ESC noted clinical input had been sought on the level of clinical need for this service, and that the Medical Devices and Human Tissue Advisory Committee (MDHTAC) expert clinical advisory group (ECAG) for Ophthalmology stated that there would be limited but definite support for suprachoroidal stent techniques, and that RANZCO stated it strongly supported supraciliary MBGS. ESC also noted the applicant stated the MINject would only be used in patients who already have the iStent available (i.e. identical population to that for 42504, and therefore no financial impact), however clinical expert input from RANZCO had stated the uveoscleral drainage pathway used by the MINject was superior in patients who cannot use the iStent due to scarring in the trabecular space, i.e., there is a clinical need for alternate MBGS devices (which MINject provides due to its alternate placement), although evidence was not provided to support this statement. ESC noted the MDHTAC ECAG commented that the proposed stent would see limited use by only very experienced glaucoma sub-specialists in patients where other techniques are contraindicated, however RANZCO foresaw broader utilisation, which ESC considered potentially indicated the MINject becoming the first-line device with trabecular stents becoming reserved for later lines of therapy. ESC considered that the advice did not align on whether the population in which the MINject would be used would include additional patients beyond those eligible for the comparator, and so the clinical place was uncertain. ESC considered the nature of clinical need for this service may be uncertain, and the difference in perspective may arise from the terminology around supraciliary stents as a subset of suprachoroidal stents. ESC considered further expert input would assist MSAC to establish the nature of clinical need for the proposed service, and the clinical place for the proposed service including any financial implications.

On safety, ESC noted that adverse events (AEs) for MINject were infrequent and generally not serious. ESC noted the main safety risk was inflammation of the anterior chamber, which occurred in 30% of patients, and that in general the evidence showed the MINject was well tolerated at 2 years. Similarly, low numbers of AEs were reported across the iStent trials, with most occurring in less than 10% of patients. However, ESC considered the intervention and comparator studies differed in the baseline IOP and medications.

ESC noted there was a lack of safety data regarding endothelial cell loss and considered that this was relevant because of the withdrawal of the CyPass device in 2019 related to loss of endothelial cells at 5 years when inserted during cataract extraction surgery. ESC noted that the ADAR did not provide evidence to address longer-term safety of the MINject. However, ESC considered that the previous safety concerns with the suprachoroidal Cypass stent were because it pressed on the cornea and reduced endothelial thickness, whereas the supraciliary MINject stent is shorter and does not press on the cornea. ESC noted CyPass's risks had not emerged until 5 years after insertion, and considered given the lack of long-term safety data there was a potential risk of AEs emerging for the MINject up to 5 years after insertion. If MSAC opts to fund supraciliary stent implantation, then it could advise safety data be collected and reported to mitigate the risk of long-term AEs emerging.

ESC considered that while the safety profiles for the MINject and iStent appeared similar, overall, there were insufficient data to draw any meaningful conclusion regarding the relative safety of MINject and iStent, although there was no reason to believe there was a current safety risk. ESC also noted that the ADAR included little discussion of the cost of managing AEs or the reduced health-related quality of life associated with them. ESC considered that understanding these impacts may help MSAC to quantify the uncertainty associated with the comparative safety profile of MINject.

Regarding effectiveness, ESC noted that reduction in IOP is the only known modifiable risk factor for glaucoma and hence change from baseline IOP was used as the primary outcome measure, along with usage of IOP-lowering medications. ESC noted there was a clinically significant decrease in IOP at 6, 12 and 24 months in the ADAR's analyses, and that the Commentary's

analyses aligning baseline IOP still showed decreased IOP at 6 months. ESC noted there was a consistent pattern of reduction in the mean number of medications used with MINInject, and improved quality of life at 2 years. ESC considered all four trial MINInject trials demonstrated a consistent trend for effect in these two key efficacy outcomes.

ESC noted the applicant claimed that the lower interstudy variability in mean IOP reduction observed for MINInject versus iStent was indicative of more reliable treatment efficacy. While the Commentary acknowledged the high degree of consistency in the performance of the MINInject, particularly in the context of demographic differences across the STAR trials (STAR-I, -III, -IV [Latin American and Indian] and STAR-II [European]), it noted that the MINInject trials were identically designed, with consistent eligibility criteria. As a result, patient populations of the STAR trials were more homogenous and thus treatment outcomes more consistent. In contrast the iStent trials varied in design, with differences in patient eligibility criteria and baseline characteristics. As such, a higher degree of statistical heterogeneity was anticipated. ESC considered that differences in the mean validity of the cross analysis compromised the comparison and made it hard to justify the conclusion of superior comparative effectiveness.

Overall, ESC considered there was very little available clinical data (including no comparative data), and the available data were single arm, observational, and of low 'GRADE' quality. There was a lack of long-term safety data regarding endothelial cell loss, which ESC considered was important as it related to the CyPass withdrawal from the market. ESC considered that while the studies overall supported the non-inferior effectiveness and safety of MINInject, the generalisability to the Australian population was unclear.

For the economics, ESC noted that the ADAR did not present a CEA but instead presented a CMA. ESC considered that a CEA or a CUA would have been more appropriate, as it would align with the MSAC Guidelines, which state that *"a cost-minimisation approach should only be used when the proposed service has been demonstrated to be noninferior to its main comparator(s) in terms of both effectiveness and safety"*. ESC noted the applicant's comments in its pre-ESC response around the choice of economic model, and considered that while a CEA would have been ideal, given the applicant was not seeking a price premium, and ESC had considered non-inferior effectiveness may be a more appropriate conclusion, that a CMA may potentially be acceptable.

ESC noted the ADAR reported an expected net saving of \$240.58 per MINInject procedure (per patient, over 2 years), and that this was based on reduced costs from lower usage IOP-lowering medication, and from reduced medication for lower ocular surface disease (OSD; dry eye disease). ESC considered that the analysis did not discuss adherence rates to IOP-lowering medications, and that the source of the quality-of-life data was uncertain. ESC also considered that the claimed cost-offsets associated with reductions in OSD medication were uncertain, as there was insufficient robust evidence to support the claim that MINInject reduced OSD treatment compared with iStent. ESC noted that the model assumed associated costs (e.g., consumables, anaesthesia) would be the same in both arms because MINInject was proposed to replace trabecular MBGS. ESC noted that the expected costs per MINInject MBGS procedure were uncertain due to the use of an en-dash instead of a minus sign, but appeared to range from an \$840 cost-offset to a \$175 cost per patient over 2 years. ESC noted the pre-ESC response stated that the analysis of incremental saving from a reduction in OSD treatment was presented as supplementary only, with the insufficiency of robust supportive data noted.

ESC also noted that no systematic review of cost-effectiveness studies was presented in the ADAR, although several recent studies in Italy, Canada and Germany reported that the stent is cost-effective. ESC also considered that this demonstrated there are sufficient data available on the natural history of glaucoma, health utilities, costs and resources, to construct a CEA or CUA. ESC considered the literature also demonstrated that the intervention was cost-effective in other

healthcare systems. ESC noted recent reviews such as Cheema & Cheema 2024¹⁵ had reported MIGS advances.

ESC noted the applicant adopted a market-share approach to estimate financial implications, based on MBS statistics for the use of standalone procedure MBS item 42504 for insertion of the comparator iStent. The ADAR's anticipated uptake of MBGS using MINInject was **Redacted**% of current MBS item 42504 procedures in year 1, increasing gradually by **Redacted**% each year. The estimate assumed a gradual uptake as more surgeons are trained to insert MINInject. ESC considered this was reasonable. ESC noted the financial analysis was based on the 85% benefit, and considered that as this was an in-hospital procedure the 75% benefit was more appropriate.

ESC noted that under the current assumptions that the proposed MBS fee was equal to the comparator, and patients who receive MINInject are simply a portion of existing patients eligible to receive a trabecular stent (i.e. patients opt to receive MINInject rather than iStent for example), then there would be no net financial impact to the MBS. However, ESC considered the advice from RANZCO suggested some patients may use the MINInject initially and then use the iStent as a second-line treatment, in which case there would be a net increase in utilisation and therefore cost to the MBS (from the stenting itself as well as associated costs such as anaesthesia that would be incurred again with the second-line stent), although no data were available to quantify this impact. However as detailed above, ESC noted the conflicting advice and considered the clinical place was uncertain.

17. Applicant comments on MSAC's Public Summary Document

On behalf of the organisations and medical specialists who have supported this application, and those surgeons who are already using MINInject in conjunction with cataract surgery, iSTAR Medical welcomes this news and expresses gratitude to MSAC for its positive recommendation for reimbursement of inserting suprachoroidal/supraciliary implants in a standalone procedure. We look forward to finalising the arrangements so that supraciliary, standalone implantation of micro-bypass glaucoma surgery (MBGS/MIGS) devices may be reimbursed under MBS item 42504.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)

¹⁵ Cheema AA, Cheema HR. The Evolution and Current Landscape of Minimally Invasive Glaucoma Surgeries: A Review. *Cureus*. 2024 Jan 12;16(1):e52183. doi: 10.7759/cureus.52183. PMID: 38264176; PMCID: PMC10804217.