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CADTH OPTIMAL USE

Optimal Use of Minimally Invasive Glaucoma Surgery: A Health Technology Assessment

Service Line:	CADTH Optimal Use
Version:	Vol. 8, no. 1b
Publication Date:	January 2019
Report Length:	399 pages

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Cite As: Optimal use of minimally invasive glaucoma surgery: a health technology assessment. Ottawa: CADTH; 2019. (CADTH optimal use report; vol.8, no.1b).

ISSN: 1927-0127

Production of this report is made possible through a financial contribution from Health Canada.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Acknowledgements

The authors would like to acknowledge Bert Dolcine for his contribution to the scoping of the Clinical Review; Dr. Yi-Sheng Chao for conducting meta-analyses; Dr. Casey Gray for verifying extracted data for the Clinical Review; Dr. Laura Weeks for providing methodological support throughout the conduct of the Patients' Perspectives and Experiences Review; Tamara Rader for facilitating patient engagement; Rebecca Zhao for her support in writing the Patients' Perspectives and Experiences Review; Ken Bond for contributing to the protocol development for the Ethical Issues Analysis; Michael Raj for leading the Environmental Scan that informed the Implementation Issues Analysis; Dr. Sohail Mulla, Dr. Joanne Kim, and Dr. Alison Sinclair for methodological support; Dr. Gino De Angelis for project management, oversight, and coordination; and Kimberley Ghosh and Paula Murray for project management support. Further, the authors would like to thank the three patient volunteers who shared their insights into and experiences of glaucoma and surgery, confidentially, for the Patients' Perspectives and Experiences Review, and the stakeholders who submitted feedback on the draft report. CADTH would like to acknowledge our colleagues at Health Quality Ontario who collaborated on this project: Anna Lambrinos for contributing to data extraction and critical appraisal, and preparation of the Clinical

Review; Lindsey Falk, Lucia Cheng, and Dr. Vivian Ng for technical review of the economic model and critical review of the draft Economic Evaluation; Corinne Holubowich for reviewing the literature search strategies; David Wells for collaboration on the Patient Perspectives and Experiences Review; Claude Soulodre and Paul Kolodziej for project management support; and Dr. Sarah McDowell and Nancy Sikich for providing final approval to the version of the report submitted for publication.

Conflicts of Interest

Dr. Cindy Hutnik has received funding from Allergan for research and for being on a user's group panel, and from Medicus for writing articles or editorials and being on an expert panel on glaucoma management. The other authors declared no conflicts of interest relevant to this report.

Abbreviations

AE	adverse event
AGI	Ahmed glaucoma implant
ALT	argon laser trabeculoplasty
BGI	Baerveldt glaucoma implant
BCVA	best-corrected visual acuity
CDVA	corrected-distance visual acuity
CI	confidence interval
CICI	Context and Implementation of Complex Interventions
COS	Canadian Ophthalmologic Society
dB	decibel
ECP	endoscopic cyclophotocoagulation
ELSI	ethical, legal, and social issues
GDD	glaucoma drainage device
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
ICUR	incremental cost-utility ratio
IOP	intraocular pressure
KDB	Kahook Dual Blade
logMAR	logarithm of the minimum angle of resolution
MICS	micro-incision cataract surgery
MIGS	minimally invasive glaucoma surgery
MMC	mitomycin C
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire – 25
OAG	open-angle glaucoma
OCCI	Ontario Case Costing Initiative
OR	operating room
Phaco	phacoemulsification
QALY	quality-adjusted life-years
QoL	quality of life
RCT	randomized controlled trial
ROBINS-I	Risk of Bias in Non-Randomized Studies of Interventions
SLT	selective laser trabeculoplasty
TM	trabecular meshwork
WTP	wilingness-to-pay
VA	visual acuity
VF	visual field

Protocol Amendments

Section	Amendment	Protocol Page Number
Clinical Review	Devices not approved and indicated for minimally invasive glaucoma surgery (MIGS) according to the Medical Devices Active Licence Listing (MDALL) at the time of protocol development (i.e., January 2018) were excluded. The Hydrus Microstent was subsequently approved by Health Canada and listed in the MDALL after publication of the protocol for this review, and therefore this device was not included as an eligible device in the protocol but is included as such in this report.	11
Patients' Perspectives and Experiences Review	Studies from non-comparable health care systems were excluded due to the interconnectedness of patients' perspectives and experiences with treatment and the health care system.	23
Patients' Perspectives and Experiences Review	A Confidence in the Evidence from Reviews of Qualitative Research (CERQual) assessment was not completed as attempts to use CERQual found that it was difficult to apply to the findings of this review, which are interpretive and not aggregative.	24
Patients' Perspectives and Experiences Review	Qualitative data-analysis software was not used, and instead memoing and diagramming was used.	25
Ethical Issues Analysis	Because no published studies were retrieved either in the commercially published or grey literature that directly examined ethical legal and social issues, bearing on glaucoma or MIGS, the selection criteria were broadened to include bodies of research and commentary that dealt with issues indirectly or analogously related to potential ethical issues identified in the Environmental Scan and through expert recommendations.	30-31

Executive Summary

Background

Issue

Glaucoma is an optic neuropathy characterized by progressive damage to the optic nerve that leads to visual impairment and potentially irreversible blindness. It is estimated that glaucoma affects more than 400,000 Canadians, with the direct cost in Canada estimated at $300 million per year. The treatment spectrum for glaucoma extends from pharmacotherapy to invasive filtration surgery, and existing treatments have strengths and limitations. The introduction of micro-invasive or minimally invasive glaucoma surgery (MIGS) devices and procedures presents a newer surgical option that may fill a previously existing gap in the glaucoma treatment paradigm, or may even be considered as the first-line therapy in some patients. As of June 2018, there were 11 MIGS devices and procedures approved for use in Canada, each of which is unique in its structure and/or mechanism of action; MIGS can be performed alone or in combination with cataract surgery. In general, there is growing demand for and use of MIGS. However, the direct and indirect costs of MIGS can be considerable, and coverage under the public health insurance plans is inconsistent across jurisdictions. Therefore, there is a need to clarify current policy on access and reimbursement related to MIGS devices and procedures. Specifically, the aim of this Health Technology Assessment was to inform the following policy questions:

What is the optimal use, including appropriate patient selection, of MIGS devices and procedures for adults with glaucoma? Should MIGS devices and procedures be funded by the public health care system?

Objectives and Research Questions

The purpose of this HTA is to inform the policy questions through an assessment of the clinical effectiveness and safety, cost-effectiveness, patients' perspectives and experiences, ethical issues, and implementation issues of MIGS devices and procedures for adults with glaucoma.

Clinical Review

1. What is the comparative clinical effectiveness of MIGS devices and procedures versus each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?
2. What is the comparative safety of MIGS devices and procedures versus each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?
3. What is the comparative clinical effectiveness of MIGS devices and procedures performed in combination with cataract surgery versus a different MIGS plus cataract surgery, filtration surgery plus cataract surgery, or cataract surgery alone for the treatment of glaucoma in adults?
4. What is the comparative safety of MIGS devices and procedures performed in combination with cataract surgery versus a different MIGS plus cataract surgery, filtration surgery plus cataract surgery, or cataract surgery alone for the treatment of glaucoma in adults?

Economic Evaluation

5. What is the cost-effectiveness of MIGS devices and procedures versus each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?

Patients' Perspectives and Experiences Review

6. What are the perspectives and experiences of patients with glaucoma regarding glaucoma and their treatment, and of their caregivers?

Ethical Issues Analysis

7. What are the major ethical issues raised by the use of MIGS devices and procedures?
8. What are the broader legal, social, and cultural considerations?

Implementation Issues Analysis

9. What are the challenges and enablers affecting the use of MIGS devices and procedures in Canada for the treatment of adult patients with glaucoma?

Clinical Evidence

Methods

A systematic review of primary studies was conducted. Online bibliographic databases were searched for comparative studies published since January 1, 2000, in English or French, and a supplementary grey literature search was also conducted. Studies were eligible for inclusion if they compared the clinical effectiveness or safety of MIGS with that of a different MIGS device or procedure, pharmacotherapy, laser therapy, or filtration surgery (including glaucoma drainage devices and Trabeculectomy), or of MIGS in combination with cataract surgery compared with cataract surgery alone, or filtration surgery in combination with cataract surgery in adults with glaucoma. Study screening was conducted in duplicate; data extraction was conducted by one reviewer and verified by a second independent reviewer. The quality of the evidence was systematically assessed in duplicate using the Cochrane Risk of Bias assessment tool for randomized controlled trials, and the Risk of Bias In Non-randomized Studies of Interventions tool for non-randomized interventions and observational studies. The overall quality of evidence for each outcome by each study design was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Narrative syntheses were conducted for each outcome, structured around each comparison and study design. The results of the included studies were pooled, using random-effects meta-analyses, if data were sufficiently homogeneous in terms of clinical, methodological, and statistical characteristics.

Findings

Thirty-two studies in 35 publications were identified that provided evidence on the clinical effectiveness or safety of MIGS versus comparators (24 unique pairwise comparisons). Across studies, the mean patient age ranged from approximately 54 to 79 years, men and women were equally represented, and the majority of patients were white. Patients with mild-to-moderate glaucoma were most commonly included, although nine studies also included some patients with advanced or severe glaucoma. All studies primarily included patients with open-angle glaucoma, and 20 studies also included some patients with different types of glaucoma (e.g., angle-closure or pseudoexfoliation). The quality of the evidence ranged from "very low" to "high" across outcomes, comparisons, and study designs. The most common limitations of the evidence were: 1) serious risk of bias that

reduced the level of confidence in the observed effects, and 2) serious imprecision (e.g., only a single study for a given comparison, no measures of variability, or wide variability leading to uncertainty about the true magnitude of the effect). Common sources of bias included: 1) bias due to confounding (e.g., treatment assignment based on patient characteristics, or significant differences between groups at baseline were not controlled), 2) bias in measurement of outcomes (e.g., no consideration of diurnal variation in intraocular pressure [IOP] or IOP being measured without medication washout, or the method of measuring number of medications or adverse events [AEs] not being reported), and 3) reporting bias (e.g., data only being reported at a subset of the time points at which they were measured). In the context of these limitations, in general, there was insufficient evidence for the comparative clinical effectiveness and safety of MIGS versus pharmacotherapy, laser therapy, different MIGS (i.e., one type of MIGS versus another), or filtration surgery. The clinical effectiveness of MIGS in combination with cataract surgery tended to be more favourable than cataract surgery alone, however findings for comparative safety were mixed. There was insufficient evidence for the comparative clinical effectiveness and safety of MIGS in combination with cataract surgery versus filtration surgery in combination with cataract surgery. Most reported AEs were considered minor in all treatment groups; however, when major AEs were observed, between-group differences were uncertain. The evidence for AEs was “very low” quality, in part because the method of measuring AEs was not reported in any study (therefore, it is uncertain whether there was any restriction on what was considered an AE, whether data on all patient-important AEs were collected, or whether information was captured systematically across patients or by convenience [e.g., in only those patients who returned to the study centre for treatment]). There was no definitive evidence regarding which MIGS might be preferable, either overall or for a subset of patients.

Economic Evidence

Methods

A Markov model was constructed to examine the cost-effectiveness of MIGS, with or without cataract surgery, compared with alternative treatments over a patient’s lifetime from a Canadian health care payer perspective. Given the heterogeneity in the 24 pairwise comparisons of MIGS versus relevant comparators that were identified in the Clinical Review, the model was adapted to provide five pairwise comparisons on MIGS to specific classes of therapy (i.e., pharmacotherapy, laser therapy, filtration surgery, cataract surgery, or filtration surgery + cataract surgery). The patient population in each analysis reflected the respective clinical studies and, as such, differed in terms of age and disease severity. The Clinical Review provided the relative treatment effects for each pairwise comparison in terms of IOP and medication reduction, in which the change in IOP was mapped to change in visual field to estimate the difference in rate of change in glaucoma progression between treatments. Health states in the model were defined according to the Hodapp-Parrish-Anderson staging for disease severity and were associated with state-specific utility weights and costs. The primary outcome was incremental cost per quality-adjusted life-years (QALYs) gained in 2018 Canadian dollars (i.e., incremental cost-utility ratio [ICUR]). Given that MIGS is a heterogeneous group of devices with potentially different relative treatment effects and costs, specific criteria were used to select the MIGS device informing the reference-case analyses for each comparison with sensitivity analyses performed on the other MIGS devices, if possible.

Findings

Given the availability of the clinical evidence, the Economic Evaluation considered MIGS in comparison with alternate therapies in patients at varying stages of the disease and was unable to examine scenarios where multiple treatment options might be suitable for particular groups of patients. The findings suggest that there are some comparisons where MIGS may be cost-effective whereas, in other cases, MIGS are unlikely to be economically attractive. Specifically, in patients with moderate glaucoma, the ICUR for MIGS compared with pharmacotherapy was found to be $18,808 per QALY, whereas MIGS was found to be dominated by laser surgery in patients with mild glaucoma (i.e., MIGS was more costly and produced fewer QALYs). If performed alongside cataract surgery, the ICUR for MIGS was $63,626 per QALY (range across different MIGS devices: $5,984 per QALY to $108,934 per QALY) compared with cataract surgery alone. The economic model found that MIGS compared with filtration surgery, with or without cataract surgery, was less costly but also resulted in fewer QALYs.

Among all models, the incremental difference in QALYs and costs were relatively small (i.e., incremental QALYs ranged from –0.07 to 0.039; incremental costs ranged from –$3,267 to $1,726). The findings were sensitive to changes in comparative treatment effects and total costs of MIGS, especially for the comparisons against more invasive surgical options (i.e., filtration surgery, with or without cataract surgery). Expected differences in QALYs between comparisons were found to be incurred throughout the analyzed time frame of the economic model; yet, there remained limited clinical evidence beyond the surrogate outcome of IOP reduction and the majority of clinical studies have so far reported follow-up of patients up to a maximum of one year. With the exception of the comparison of MIGS (Hydrus Microstent) + cataract surgery compared with cataract surgery alone, which was based on “high” quality evidence, the rest of the comparisons were informed by clinical studies with evidence deemed to be of lower quality. Adequately powered studies using clinically important outcome measures with longer follow-up periods may be useful to confirm and validate the findings of the Economic Evaluation. Incremental costs between comparators occurred early in the model and were largely driven by initial surgery-related costs. Variability in costs exists between settings and jurisdictions, and in some instances, uncertainty remains regarding the true costs of MIGS as they are not currently performed in certain jurisdictions. Caution is therefore required in interpreting these findings given the uncertainty in relative efficacy and cost; however, the economic results do suggest that, if used indiscriminately, MIGS may not always be the most cost-effective treatment option in certain patient groups.

Patients’ Perspectives and Experiences Evidence

Methods

A systematic review and thematic synthesis of primary qualitative research describing the perspectives and experiences of patients with glaucoma, and those of their caregivers, was conducted. Patient engagement occurred throughout the project and involved conversations with three female patients with glaucoma, two of whom had undergone MIGS.

Findings

Fifteen included publications were identified that reported on qualitative research on patients’ and caregivers’ perspectives and experiences of glaucoma. These studies were critically appraised as being of low quality.

The results of the thematic synthesis centred around patients' experiences and perceptions of glaucoma. A diagnosis of glaucoma was unexpected, typically patients explained vision changes as part of normal aging, not as a prompt to seek vision care. This means that those without routine vison care may be more at risk for being diagnosed with more advanced glaucoma and therefore be ineligible for MIGS. Pharmacotherapy in the form of eye drops was disruptive to patients' lives. Despite a range of creative and committed responses, patients with comorbidities and busy lives with travel or lack of routine made adherence difficult. Reducing the number and frequency of medications was valued by patients. Patients expressed a range of views on glaucoma surgeries, from being a last resort to freedom from eye drops. Some may be conservative in assuming the risks of a surgery where blindness is a possibility. Patients experienced glaucoma as an illness, not as a disease. This means that a patient's experience of glaucoma was shaped by, but not reducible to, their clinical condition. While surgical treatments can offer patients improved clinical outcomes, patients still worried about the need to use additional medications or future surgery and the need for vigilance about the return of elevated IOP, pointing to the lingering impact of glaucoma.

Ethics Evidence

Methods

A literature search was performed using a peer-reviewed search strategy, with methodological filters applied to limit retrieval to studies related to ethical, legal, and social issues (ELSI). The search was limited to English- or French-language publications. Articles, studies, and reports were included if they explicitly and specifically raised ELSI issues related to the central question of this HTA as well as literature that may point to potential ethical issues. No published studies were retrieved either in the commercially published or grey literature that directly examined ELSI issues bearing on glaucoma or MIGS. For this reason, the selection criteria were broadened to include bodies of research and commentary that dealt with issues indirectly or analogously related to potential ethical issues identified through expert recommendations and through a CADTH Environmental Scan titled *Minimally Invasive Glaucoma Surgery: Implementation Considerations*.

Findings

Two major findings of fact bear on the analysis of ethical and social aspects of the optimal use of MIGS in Canada. First, there is a disparity between the existing quality of evidence on the clinical effectiveness of MIGS and the belief in its value manifested in the adoption of MIGS by Canadian specialists and hospitals to date. Second, current usage of MIGS in Canada is not strongly evidence-based, standardized, or personalized to the needs of patients. A major category of ethical concerns about the use of MIGS in Canada is equity of access: whether and under what conditions there can be equitable access for Canadians treated in different health care systems and facilities; for those living in rural and remote versus more urban locations; for those with different economic capacities to incur out-of-pocket costs associated with MIGS; and for those belonging to various racial or ethnic groups. A second set of concerns has to do with the status of MIGS as a surgical innovation. These concerns require ensuring that conflicts of interest in the use of MIGS are avoided and that evidence on outcomes is gathered and assessed. They also demand that professionals carry out their responsibility to ensure that patients are fully informed about options, evidence, and other relevant issues surrounding their potential choice of MIGS.

Implementation Issues Evidence

Methods

Methodology and results for the implementation analysis were informed by the CADTH Environmental Scan titled *Minimally Invasive Glaucoma Surgery: Implementation Considerations*. Implementation-related information regarding MIGS devices and procedures was identified by searching bibliographic databases and grey literature between January 1, 2000, and October 17, 2017, with regular alerts run until June 1, 2018. Both study selection and data abstraction were performed by one reviewer. Consultations with targeted key informants (identified using CADTH's Implementation Support and Knowledge Mobilization team or through referrals) were performed using developed research questions.

Findings were analyzed using predetermined categories identified by the Context and Implementation of Complex Interventions framework from INTEGRATE-HTA.

Findings

In total, 21 key informants were interviewed and data from 21 relevant publications were used to inform the analysis.

The majority of provinces and territories do not have MIGS devices or procedures in the physician schedule of benefits, and they are not an insured benefit. MIGS are often provided at a cost to the facility or at a cost to the patient themselves. This can pose ethical issues as there are geographic inequalities in access, and further, that access to MIGS can be based on ability to pay versus need. Funding challenges, high start-up costs, and finite budgets for facilities with the ability to provide MIGS devices can be prohibitive to their implementation.

Geographically, patients who live closer to a facility providing MIGS are more likely to be able to receive the surgery. However, not all MIGS devices and procedures are available at every facility; therefore, proximity to a glaucoma centre is not necessarily a facilitator in all cases.

Having strong ophthalmology leadership and operating rooms that favour new technologies such as MIGS can be an enabler to their use and an enabler for acquiring adequate funding. In comparison to smaller regions or facilities, larger or more urban regions may be more able to attract glaucoma specialists who have the ability to perform MIGS. However, the relative lack of trained ophthalmologists and the lack of appropriate credentialing or standards create barriers for implementation of MIGS devices and procedures. Currently, manufacturers provide much of the training for MIGS. Despite this, and despite support from glaucoma professional societies (including the Canadian Glaucoma Society and Canadian Opthalmological Society in the form of a 2017 MIGS position statement indicating MIGS for use in patients with mild-to-moderate glaucoma), there are a lack of clinical practice guidelines detailing appropriate patient selection and use of MIGS devices and procedures. This can contribute to the uncertainty of the placement of MIGS in the glaucoma treatment paradigm.

There was a gap in the literature regarding socioeconomic, sociocultural, political, legal, or epidemiological barriers and enablers associated with MIGS devices and procedures. Additionally, the responses of the 21 informants who contributed to the report reflected personal opinions and experiences with MIGS, and not all jurisdictions responded to the request for an interview by the consultation deadline, therefore this assessment may not be fully representative of all facilities, jurisdictions, and stakeholders.

Conclusion

Overall, there was insufficient evidence for the comparative clinical effectiveness and safety of MIGS versus pharmacotherapy, laser therapy, different MIGS (i.e., one type of MIGS versus another), or filtration surgery. The clinical effectiveness of MIGS in combination with cataract surgery tended to be more favourable than cataract surgery alone; however, findings for comparative safety were mixed. There was insufficient evidence for the comparative clinical effectiveness and safety of MIGS in combination with cataract surgery versus filtration surgery in combination with cataract surgery. The clinical effectiveness conclusions were based largely on indirect outcomes (i.e., IOP and number of medications as surrogates for visual field and quality of life, respectively); particularly in the context of such inconclusive clinical outcomes, increased attention to patient-important outcomes (e.g., health-related quality of life) is imperative. Most AEs were considered minor; however, between-group differences were unclear when major AEs occurred.

In terms of cost-effectiveness, MIGS seemed to offer more clinical benefit at a higher cost when compared with pharmacotherapy or when performed in combination with cataract surgery instead of cataract surgery alone. Results were sensitive to costs associated with MIGS and the purported long-term benefits of MIGS. These findings highlight the fact that specific situations may exist whereby MIGS may be cost-effective but, if used indiscriminately, MIGS may not always be the cost-effective treatment option for certain patients.

Current treatments for glaucoma in the form of eye drops are highly disruptive for patients who welcome the opportunity to reduce or eliminate the need to use eye drops. Patients' perceptions and experiences of glaucoma were highly shaped by the societal understandings and awareness of glaucoma and of blindness. While treatments may reduce IOP and slow the progression of their glaucoma, once diagnosed, patients move through the world with glaucoma. As glaucoma is a chronic condition, patient–provider relationships are central to patients' experiences with glaucoma treatment and provide an opportunity to assist patients to become acquainted with glaucoma, to improve adherence, and to adjust to vision changes.

Ethically and socially relevant issues include the need for guidelines to help institutions and surgeons fairly allocate MIGS under conditions of scarcity; concerns about public coverage versus private payment for MIGS, as well as diverging views of MIGS as an "optional upgrade" or a medical need; and concerns about equitable access to MIGS for patients living in rural and remote locations and for patients from certain racialized groups. Ethical concerns related to the context of surgical innovation include conflicts of interest, assignment of responsibility for tracking and reporting outcomes of MIGS usage, and challenges defining and carrying out surgeons' responsibility to enable informed patient consent with respect to the potential use of MIGS.

Implementation of MIGS in Canada is a multi-factorial issue, including factors such as funding models, organization, and professional considerations. Currently, access is limited for many Canadians due to geography or setting, restricted supply of the technology, or slow uptake of the technology by providers.

Although MIGS are categorized as a particular class of interventions, each is unique in terms of its structure and mechanism of action, and may reasonably be anticipated to have different clinical effectiveness, safety, and cost-effectiveness profiles. There was insufficient evidence to offer specific conclusions regarding individual MIGS devices and procedures, and there was no definitive evidence regarding which MIGS might be preferable, either overall or for a subset of patients.

1. Introduction

1.1 Background and Rationale

Glaucoma is an optic neuropathy characterized by progressive damage to the optic nerve that leads to visual impairment and potentially irreversible blindness.[1-3] Glaucoma is sometimes called the “silent thief of sight” because its symptoms are often not apparent until irreversible damage to the optic nerve fibres has been done.[4] It is estimated that glaucoma affects more than 400,000 Canadians, and the direct cost in Canada is estimated at $300 million per year.[5,6] Risk factors for glaucoma include elevated intraocular pressure (IOP; i.e., pressure inside the eyes), increasing age, a family history of glaucoma, race, and comorbidities including diabetes, hypertension, and hypothyroidism.[3,4,7]

Glaucoma is a pressure-sensitive optic neuropathy with elevated IOP being the most important and only modifiable risk.[3,8] When IOP becomes elevated, it can compress and damage the optic nerve;[1,9] for every 1 mm Hg increase in IOP, there is a 10% higher risk of both development and progression of glaucoma.[10] IOP can become elevated when the balance between production and drainage of fluid that nourishes the lens and cornea, known as aqueous humour, is disrupted. Open-angle glaucoma (OAG) occurs when the system responsible for draining fluid from the eye (i.e., Schlemm’s canal, including trabecular meshwork [TM]) is anatomically open, but functioning sub-optimally; angle-closure glaucoma occurs when the fluid draining system is anatomically blocked.[8] OAG represents the most common form of the condition.[4,11]

In this regard, the most common treatment approach seeks to lower IOP by either reducing the production of aqueous humour or enhancing its drainage to delay the progression of glaucoma and prevent potential blindness.[8,12] Treatment can slow or halt the progression of the condition but cannot reverse damage that has already been done to the optic nerve.[4]

The treatment spectrum for lowering IOP extends from pharmacotherapy (e.g., eye drops) or laser therapy as the first-line treatment to invasive filtration surgeries, such as Trabeculectomy (i.e., removal of part of the TM and adjacent structures) and implantation of aqueous shunts.[13,14] Challenges associated with pharmacotherapy include ineffective use (e.g., under- or overdosing, incorrect timing, or administration),[15,16] local or systemic side effects (e.g., irritation) or toxicity,[17,18] and considerable lifetime costs.[19] Laser surgery may be less effective than pharmacotherapy, and can be associated with ocular discomfort, IOP spikes, and the need for repeat procedures.[20,21] Although filtration surgeries are well established and generally effective,[22] they carry the risk of potentially dangerous intraoperative and post-operative complications (such as hypotony [i.e., excessively low IOP], infection, inflammation, vision loss, cataract, and need for subsequent surgery),[4,13,23,24] have a long recovery period,[25] and, because of their invasive nature, may affect subsequent surgery if required due to scar tissue formation.[23] The filtration surgical options have typically been used in advanced glaucoma cases or when targeting a very low IOP as a treatment outcome because of the associated substantial risks.[23,26] Thus, there are strengths and limitations associated with existing treatment options.

The advent of micro-invasive or minimally invasive glaucoma surgery (MIGS) devices and procedures presents a newer surgical option that may fill a previously existing gap between pharmacotherapy or laser therapy and the invasive filtration surgeries.[13,26-29] The FDA and the American Glaucoma Society jointly proposed a working definition that describes MIGS as devices and procedures that intend to lower IOP by improving outflow of eye fluid using

either an ab interno (from inside the eye) or ab externo (from outside the eye) approach, with limited or no dissection of the sclera and minimal or no manipulation of the conjunctiva.[30-32] Other definitions[23,29] are generally consistent with the FDA–American Glaucoma Society definition, though they may differ in some aspects (e.g., inclusion of ab interno devices and procedures only).[23] Regardless, certain features and qualities are commonly associated with MIGS devices and procedures, including the following:

- They are anticipated to have a better safety profile and more rapid recovery than the traditional, invasive glaucoma surgeries.
- They are generally indicated for treatment of mild-to-moderate glaucoma cases.
- While they can be standalone surgeries, they are often performed in conjunction with cataract surgery to help maximize clinical effectiveness and cost efficiency and to reduce the risk of causing a cataract in a patient with phakic (i.e., natural) intraocular lenses.[12,13,19,23,26,27,32]

Generally, MIGS devices and procedures are aimed at, and evaluated in, OAG patients.[26,28,33-35] While MIGS was initially positioned as filling a gap in the spectrum of treatment, the treatment paradigm is shifting and, if both clinically effective and cost-effective, there is the potential for MIGS to become the first-line therapy for some patients.[22,36] The characteristics of patients for whom MIGS devices and procedures would be most clinically effective, cost-effective, and acceptable remain to be established.

As of November 2018, there were 11 MIGS devices and procedures approved for use in Canada (listed in Appendix 1); one device (the CyPass Micro-Stent) was voluntarily withdrawn from the global market by the manufacturer in August 2018 based on data from a long-term five-year safety study.[37,38] Although MIGS are categorized as a particular class of interventions, each MIGS is unique in its structure and/or mechanism of action, and different MIGS may have different clinical effectiveness or safety profiles. The MIGS options may be grouped according to the approach for reducing IOP:

- reducing aqueous production (i.e., endoscopic cyclophotocoagulation)
- increasing trabecular outflow by bypassing the TM using:
  - tissue ablation or removal (i.e., Trabectome and Kahook Dual Blade)
  - a device (i.e., iStent, iStent Inject, or Hydrus Microstent)
  - 360º suture (i.e., gonioscopy-assisted transluminal Trabeculotomy)
- increasing uveoscleral outflow via suprachoroidal shunts (i.e., CyPass Micro-Stent)
- creating a subconjunctival pathway for filtration (i.e., XEN 45 Gel Stent, XEN 63 Gel Stent, and XEN 140 Gel Stent).

As mentioned, MIGS may be performed alone or in conjunction with cataract surgery (e.g., phacoemulsification), which also independently lowers IOP.[31]

In general, there is growing demand for and use of MIGS.[27,36] However, the cost of MIGS can be considerable, and coverage under the public health insurance plans is inconsistent across jurisdictions.[39] This inconsistency includes reimbursement and inclusion of MIGS in the physician schedule of benefits in some jurisdictions (such as Alberta and Quebec), and not in other jurisdictions (such as Ontario and Manitoba). Additionally, as reimbursement decisions can be facility-specific, one facility may provide or cover the cost of a type of MIGS, and another in the same jurisdictional area may not. Therefore, there is a need to

clarify current policy on access and reimbursement related to MIGS devices and procedures.

1.2 Policy Question

What is the optimal use, including appropriate patient selection, of MIGS devices and procedures for adults with glaucoma? Should MIGS devices and procedures be funded by the public health care system?

2. Objective

The purpose of this Health Technology Assessment (HTA) was to address the policy questions through an assessment of the clinical effectiveness and safety, cost-effectiveness, patients' perspectives and experiences, ethical issues, and implementation issues of MIGS devices and procedures for adults with glaucoma.

2.1 Research Questions

This HTA informs the policy question by addressing the following research questions:

Clinical Review

1. What is the comparative clinical effectiveness of MIGS devices and procedures versus each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?
2. What is the comparative safety of MIGS devices and procedures versus each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?
3. What is the comparative clinical effectiveness of MIGS devices and procedures performed in combination with cataract surgery versus a different MIGS plus cataract surgery, filtration surgery plus cataract surgery, or cataract surgery alone for the treatment of glaucoma in adults?
4. What is the comparative safety of MIGS devices and procedures performed in combination with cataract surgery versus a different MIGS plus cataract surgery, filtration surgery plus cataract surgery, or cataract surgery alone for the treatment of glaucoma in adults?

Economic Evaluation

5. What is the cost-effectiveness of MIGS devices and procedures versus each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?

Patients' Perspectives and Experiences Review

6. What are the perspectives and experiences of patients with glaucoma regarding glaucoma and their treatment, and of their caregivers?

Ethical Issues Analysis

7. What are the major ethical issues raised by the use of MIGS devices and procedures?
8. What are the broader legal, social, and cultural considerations?

Implementation Issues Analysis

9. What are the challenges and enablers affecting the use of MIGS devices and procedures in Canada for the treatment of adult patients with glaucoma?

3. Clinical Review

A systematic review of primary studies was conducted to address the four clinical research questions:

Research Question 1:	What is the comparative clinical effectiveness of MIGS devices and procedures versus each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?
Research Question 2:	What is the comparative safety of MIGS devices and procedures versus each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?
Research Question 3:	What is the comparative clinical effectiveness of MIGS devices and procedures performed in combination with cataract surgery versus a different MIGS plus cataract surgery, filtration surgery plus cataract surgery, or cataract surgery alone for the treatment of glaucoma in adults?
Research Question 4:	What is the comparative safety of MIGS devices and procedures performed in combination with cataract surgery versus a different MIGS plus cataract surgery, filtration surgery plus cataract surgery, or cataract surgery alone for the treatment of glaucoma in adults?

A protocol for the systematic review (CRD42018082223)[40] was written a priori and followed throughout the review process.

3.1 Methods

3.1.1 Literature Searches

The literature search was performed by an information specialist using a peer-reviewed search strategy. The clinical search strategy is presented in Appendix 2.

Information was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates, Embase (1974–), the Cochrane Central Register of Controlled Trials via Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were glaucoma, minimally invasive glaucoma surgery, and minimally invasive glaucoma surgical devices.

Retrieval was limited to documents added to the databases since January 1, 2000. Conference abstracts were excluded from the search results. The search was limited to English- or French-language publications.

The initial searches were completed in November 2017. Regular alerts were established to update the searches until the publication of the final report. Regular search updates were

performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review were to be incorporated into the analysis if they were identified prior to the completion of the stakeholder feedback period of the final report. Any studies that were identified after the stakeholder feedback period were to be described in the discussion, with a focus on comparing the results of these new studies to the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, systematic review repositories, economics-related resources, public perspective groups, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

The list of included studies was posted online for 10 business days, during which time stakeholders submitted additional publications for consideration.

3.1.2 Selection Criteria

Studies were included if they were published in English or French and met the criteria presented in Table 1.

Studies with mixed populations, that is, comprising both individuals who met and those who did not meet the eligibility criteria, were considered eligible for inclusion if the results pertaining to the population of interest were reported separately. If results for the population of interest were not reported separately, studies with a mixed population were considered eligible if 80% or more of the population met the inclusion criteria.

Regarding interventions specifically, devices not approved and indicated for MIGS according to the Medical Devices Active Licence Listing (MDALL) at the time of protocol development (i.e., January 2018) were excluded. The Hydrus Microstent was subsequently approved by Health Canada after publication of the protocol for this review and listed in the MDALL, and therefore this device was not included as an eligible device in the protocol[40] but is included as such in this report. The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 (due to five-year data from a long-term safety study);[37,38] however, at the time of report publication, this device was still active in the MDALL and is therefore included in this report.

If there were multiple publications from the same study, the older publications were not eligible for inclusion unless they provided additional information on outcomes of interest (e.g., different follow-up time points).

Table 1: Inclusion Criteria Clinical Review

Population	Adults (i.e., mean age of ≥ 18 years) diagnosed with glaucoma **Exclusions:** • Adults with juvenile-onset/congenital glaucoma • Adults with ocular hypertension but no evidence of optic nerve damage or formal diagnosis of glaucoma • Animal or ex vivo populations
Interventions	**Questions 1 and 2:** • The following MIGS:[a] ○ Approach: Reducing aqueous production ▪ ECP ○ Approach: Increasing trabecular outflow by bypassing the TM using tissue ablation/removal ▪ Trabectome ▪ Kahook Dual Blade ○ Approach: Increasing trabecular outflow by bypassing the TM using a device ▪ iStent (first generation) ▪ iStent Inject (second generation) ▪ Hydrus Microstent ○ Approach: Increasing trabecular outflow by bypassing the TM via 360º suture ▪ GATT ○ Approach: Increasing uveoscleral outflow via suprachoroidal shunts ▪ CyPass Micro-Stent[b] ○ Approach: Creating a subconjunctival pathway for filtration ▪ XEN 45 Gel Stent ▪ XEN 63 Gel Stent ▪ XEN 140 Gel Stent **Questions 3 and 4:** The above MIGS devices and procedures performed in combination with cataract surgery (e.g., phacoemulsification or MICS)
Comparators	**Questions 1 and 2:** • A different[c] MIGS device or procedure • Pharmacotherapy alone • Laser therapy (e.g., excimer laser Trabeculotomy or selective laser trabeculoplasty) • Filtration surgery (e.g., Trabeculectomy or aqueous shunt implantation) **Questions 3 and 4:** • A different MIGS device or procedure performed in combination with cataract surgery (e.g., MIGS + phacoemulsification or MICS) • Filtration surgery performed in combination with cataract surgery (e.g., Phacotrabeculectomy) • Cataract surgery (e.g., Phacoemulsification or MICS) alone
Outcomes[d]	**Questions 1 and 3 (Clinical Effectiveness):** **Primary:** • Health-related QoL **Secondary:** • IOP (e.g., absolute level, reduction, or proportion of patients meeting target of ≤ 21 mm Hg) • Number of glaucoma medications used • Vision-related QoL • Visual field loss, visual impairment, visual acuity **Questions 2 and 4 (Safety):** Adverse events and complications (e.g., transient IOP fluctuation, infection, hyphema, hypotony, device occlusion or malposition, need for additional procedure[s], or cataract formation)

Study Design	**Comparative study designs:** • Randomized controlled trials • Non-randomized controlled clinical trials • Cohort studies[e] • Case-control studies **Exclusions:** • Case reports • Case series • Review articles • Editorials, letters, and commentaries • Studies of any design published as conference abstracts, presentations, or thesis documents
Time Frame	2000 to present

ECP = endoscopic cyclophotocoagulation; GATT = gonioscopy-assisted transluminal trabeculotomy; IOP = intraocular pressure; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; QoL = quality of life; TM = trabecular meshwork.

[a] MIGS devices and procedures that were approved for use by Health Canada were eligible for inclusion.

[b] The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the Medical Devices Active Licence Listing and is therefore included in this report.

[c] "A different MIGS" means any MIGS device or procedure compared with any other MIGS device or procedure (i.e., MIGS compared with each other).

[d] All outcomes were considered to be of "critical" importance[41] based on the informal scoping review that informed this project and on consultation with a clinical expert.

[e] Cohort studies were defined as studies in which participants were sampled on the basis of exposure (and contained exposed and unexposed groups) and in which outcomes were assessed at follow-up.[42] This is distinct from case series studies, in which participants are sampled on the basis of the presence of an outcome, or of both an exposure and outcome, and from case-control studies in which there is a control group.[42] Only study designs providing comparative evidence were eligible for inclusion.

3.1.3 Selection Method

Two reviewers independently screened titles and abstracts of all retrieved citations against eligibility criteria (Table 1). Exclusion by both reviewers was required for a record to be excluded at the title and abstract level. Full-text versions of all other articles were retrieved for the second level of screening. The same reviewers independently examined all full-text articles, and consensus was required for inclusion in the review. Discrepancies between reviewers were resolved by discussion between the reviewers and by consultation with a clinical expert if needed. Study selection was conducted using DistillerSR online software[43] using standardized screening forms.

3.1.4 Quality Assessment and Data Extraction

Quality Assessment: Individual Studies

The quality of the primary studies was systematically assessed using the methods described in the Cochrane Risk of Bias assessment tool for randomized controlled trials (RCTs)[44] and the Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool for non-randomized interventions and observational studies.[45]

The Cochrane Risk of Bias tool allowed for the assessment of seven sources of bias (selection bias due to inadequate randomization, selection bias due to inadequate allocation concealment, performance bias, detection bias, attrition bias, reporting bias, or other sources of bias). For each item, a judgment of "low," "high," or "unclear" was assigned.[44]

The ROBINS-I tool allowed for the assessment of risk of bias across 34 potential items in seven domains (i.e., bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, or selection of reported result). Each item was answered as "yes," "probably yes,"

"probably no," "no," and "no information." Risk of bias for each domain in each study was assessed as "low," "moderate," "serious," or "critical" by the reviewer, in accordance with ROBINS-I guidance.

For sources of bias that may differ across outcomes (i.e., detection, attrition, and reporting bias in RCTs; bias in measurement of outcomes, due to missing data or selective reporting in all other study designs), the risk of bias was assessed (and reported) for individual outcomes within individual studies. If the risk of bias differed across outcomes within a given study, the least favourable (i.e., most severe) rating was included in the overall summary rating for the risk of bias for that study.

The quality assessment was conducted by two independent reviewers, with any disagreements resolved by discussion with a third reviewer, if required. The results of the risk of bias assessments were used as one component of evaluating the overall quality of evidence.

Quality Assessment: Overall Body of Evidence

The quality of evidence for each outcome by each study design was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[46] According to GRADE, evidence from RCTs begins with a rating of "high" quality, but can be downgraded (to "moderate," "low," or "very low") if there is serious or very serious risk of bias,[47] inconsistency (e.g., unexplained heterogeneity in the effect),[48] indirectness (e.g., use of a surrogate measure instead of a direct measure of an outcome),[49] imprecision (e.g., wide confidence intervals [CIs] leading to uncertainty about the true magnitude of the effect),[50] or publication bias,[51] because these characteristics reduce the certainty in the estimated effect. Evidence from all other study designs begins with a "low" quality rating, but can be upgraded if there is no cause to downgrade and if there is a large magnitude of effect, a dose-response gradient, or the presence of plausible confounders or biases that would decrease an apparent effect,[52] because these characteristics increase the confidence in the estimated effect.

The risk of bias across studies of a given study design contributing to a particular outcome was judged to be "serious" or "very serious" if plausible bias was identified (in the Cochrane or ROBINS-I assessments) that raised some doubt or seriously weakened the level of confidence in the results. For RCTs, if the only cause for concern was a failure to mention whether allocation to the treatment groups was concealed, this was considered as "no serious risk of bias" because this was deemed to likely be caused by poor reporting.[53]

For studies that were pooled in meta-analysis, inconsistency was judged to be "serious" if unexplained heterogeneity was interpreted as "moderate" (I^2 values of 30% to 60%), or as "very serious" if heterogeneity was interpreted as "substantial" or "considerable" (I^2 values of 50% to 90% or ≥ 75%).[44,48] For studies in which findings were synthesized narratively, inconsistency was judged to be "serious" or "very serious" if there was unexplained heterogeneity in the direction of the effect (e.g., comparison favouring the intervention in one study and the comparator in another).[48,54]

If there was only one study contributing to an outcome for a particular intervention and comparison, this was conservatively considered as "serious imprecision" and was evaluated in the context of the other characteristics of that study.[50,55]

Quality assessments were performed by one reviewer and verified by a second reviewer, and were presented in GRADE evidence profile tables.[56] Quality assessments were used to provide explicit judgments about the certainty in the evidence.

Data Extraction

Data extraction for included studies was conducted in Microsoft Word. Data extraction forms were piloted by a clinical reviewer and two methodologists (CADTH Scientific Advisors). Relevant information was extracted, where available, including:

- study characteristics (e.g., first author's name, publication year, country where the study was conducted, funding sources)
- methodology (e.g., study design, analytical approach, follow-up duration, inclusion and exclusion criteria)
- population (e.g., number of patients and/or eyes, age, sex, race, type of eyes, type of glaucoma, glaucoma severity/stage, previous ocular procedure[s], relevant comorbidities, and baseline characteristics)
- intervention (i.e., type and number of MIGS, and whether performed alone or in conjunction with cataract surgery)
- comparator
- results and conclusions (including exact *P* values, where available) regarding the outcomes (and their method of measurement, where available) and subgroups of interest
- to which research question(s) the study was relevant.

Data extraction was completed by one reviewer and checked for accuracy by a second reviewer. Data from figures were extracted if explicit numerical data were reported. If relevant data were missing from included studies, attempts were made to contact the corresponding authors of these studies to obtain missing information. If numerical values were discrepant throughout a study (e.g., different values reported in the abstract, results tables, and/or results text), all values were extracted and reported. If a study was reported in multiple publications, the most complete data (i.e., largest sample size) was extracted for each outcome and time point, even if there was a later publication. Articles reporting longer follow-up tended to report interim data only for the subset of patients with longer follow-up. Study findings were considered statistically significant at $P < 0.05$.

3.1.5 Data Analysis Methods

Data analysis was conducted separately for each outcome. Within each outcome, studies were grouped first by intervention and comparator, and then by study design. If relevant statistical comparisons were not conducted in the primary studies, this was explicitly stated, the direction of findings was summarized subjectively where possible in the text (e.g., whether the outcome variable changed numerically over time or was numerically different between groups), and overall findings were described as "uncertain" or "unclear." If findings were different at incremental follow-up time points, the longest available follow-up time point was used in describing the overall findings (regardless of the end point selected by the authors). The planned unit of analysis was the participant; data were extracted as reported in individual studies (i.e., by patients or eyes).

Narrative Syntheses

Narrative syntheses were conducted for each outcome, structured around each comparison and study design. This included the presentation of study characteristics and findings within summary tables (Appendix 8 to Appendix 13). The direction and size of observed effects were summarized across studies.

For safety outcomes, adverse events (AEs) and complications were grouped together and categorized as “major” (appreciable, clinically relevant; e.g., sight-threatening) and “minor” (notable, but relatively inconsequential from a clinical or patient perspective), based on the advice of a clinical expert consulted on this review. A complete list of AEs and their categorization as “major” or “minor” is found in Table 27, Appendix 3. Note that categorizations were based on the specific AEs and complications, and not on anticipated downstream effects. For example, “stent not visible” was categorized as a minor AE; if this led to a secondary surgical procedure, this secondary procedure was categorized separately as a major complication. Categorization was done from a clinical or patient perspective; economic or other perspectives were not considered. In cases where there was insufficient detail to confidently ascribe a level of severity, assumptions were made based on clinical experience. For example, although cystoid macular edema can be sight-threatening if persistent, it is usually temporary and resolves with topical medication and observation; therefore, cystoid macular edema was categorized as a minor complication. In some studies, the number of patients experiencing an AE or complication was reported, whereas in other studies the number of unique AEs or complications was reported; in both cases, some individuals may have experienced more than one AE or complication. Results were described as reported in individual studies. For brevity, all AEs and complications were described together as “AEs.”

Meta-Analyses

The results of the included studies were pooled, using random-effects meta-analyses, if data from at least two studies were sufficiently homogeneous in terms of clinical, methodological, and statistical characteristics.[57] Clinical and methodological heterogeneity were assessed in consultation with a clinical expert and two methodologists (CADTH Scientific Advisors), and considered patient and study design factors that might be expected to affect the clinical effectiveness and/or safety of MIGS (e.g., severity or stage of disease, or type of MIGS and comparator). Separate analyses were conducted for randomized and non-randomized studies; results from randomized and non-randomized studies were not pooled.

Where appropriate, continuous outcomes were pooled using mean differences and corresponding 95% CIs. Forest plots were created for all individual summary estimates. Meta-analyses were carried out using R environment (version 3.4.2) and RStudio (version 1.0.143). Additional details on planned analyses that were not conducted due to a lack of applicable data are found in the protocol.[40]

Heterogeneity and Subgroup or Meta-Regression Analyses

Statistical heterogeneity was assessed using graphical presentations (e.g., forest plots) and calculations of Cochran’s chi-square test and the I^2 statistic, which quantifies the variability in the effect estimates due to heterogeneity rather than chance (i.e., sampling error). Heterogeneity was interpreted according to the guidance in the Cochrane handbook, as follows: I^2 values < 40% might not be important (i.e., considered “low”), values of 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial

heterogeneity, and ≥ 75% may represent considerable heterogeneity.[44] Heterogeneity was considered statistically significant if the *P* value for Cochran's chi-square test was < 0.10.[44]

If possible, depending on the amount of available data and the degree of observed statistical heterogeneity, subgroup or meta-regression analyses were planned to explore reasons for heterogeneity. The subgroups of interest to be examined in exploratory analyses were:

- treatment-naive versus treatment-experienced (e.g., previous laser therapy, previous MIGS, previous filtration surgery, or current/previous pharmacotherapy)
- primary versus secondary glaucoma
- open-angle versus angle-closure glaucoma
- number of MIGS devices (e.g., one, two, or three iStents)
- severity or stage of glaucoma (e.g., early, moderate, or advanced)
- phakic versus pseudophakic eyes.

Sensitivity Analyses

Sensitivity analyses were considered to evaluate the robustness of findings by methodological and statistical factors, including the impact of different study designs (e.g., RCTs versus cohort studies), different population compositions (i.e., pure versus "mixed" samples, with at least 80% of the included sample meeting the population inclusion criteria), varying study quality assessments, types of analysis (e.g., unadjusted versus adjusted; studies in which means were reported versus those in which means were estimated from medians), and effect measures (e.g., relative risks versus odds ratios). Recognizing that the surgical and/or clinical setting may change over time, sensitivity analyses by study publication date were also considered.

Publication Bias

If there were 10 or more included studies of a given study design and a particular outcome, assessments of publication bias were planned using funnel plots and Egger's regression test and Begg's rank correlation test.[44]

3.2 Results

3.2.1 Selection of Primary Studies

A total of 2,349 citations were identified in the literature search. Nine potentially relevant reports were retrieved from other sources (i.e., search alerts or handsearching). Following screening of titles and abstracts, 2,271 citations were excluded and 87 were retrieved for full-text review. Of these potentially relevant articles, 52 publications were excluded for various reasons, and 32 studies in 35 publications met the inclusion criteria and were included in this review. No unique publications that met the inclusion criteria were submitted by stakeholders. Nine studies in 10 publications were relevant to research questions 1 and 2;[25,36,58-65] and 23 studies in 25 publications were relevant to research questions 3 and 4.[34,66-89] The study selection process is outlined in Appendix 3 using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram. Lists of included and excluded citations, with details describing the rationale for those excluded, are presented in Appendix 5 and Appendix 6, respectively.

Heterogeneity and Decisions Regarding Meta-Analyses

Six studies (in eight publications)[34,66-68,71,78,79,88] were considered to have sufficient methodological, clinical, and statistical homogeneity to be pooled in various meta-analyses. In all cases, absolute values of outcome variables were pooled at follow-up time points, based on the availability of the data. Findings from all other studies were synthesized narratively. The complete list of included studies and the comprehensive rationale regarding meta-analyses is found in Appendix 7. In brief, sources of heterogeneity included differences across studies in:

- population characteristics (e.g., type and severity of glaucoma, baseline IOP)
- interventions and comparators (i.e., 24 different comparisons across the 32 included studies)
- outcomes (e.g., reported as absolute values, absolute or relative change from baseline; or measured using different methods)
- time points (e.g., different follow-up duration)
- study design.

Due to the limited amount of available data, subgroup analyses, meta-regressions, sensitivity analyses, and objective assessments of publication bias were not possible.

3.2.2 Study Characteristics

Because distinct studies inform the different research questions, study characteristics are presented separately for the clinical effectiveness and safety of MIGS alone versus comparators (research questions 1 and 2) and of MIGS in combination with cataract surgery versus comparators (research questions 3 and 4). Additional details regarding the characteristics of included studies are provided in Appendix 8 and Appendix 10.

Study Design, Year of Publications, and Funding

MIGS Versus Comparators (Research Questions 1 and 2)

Three RCTs (in four publications),[36,58-60] one non-randomized controlled clinical trial,[61] two prospective cohort studies,[25,62] and three retrospective cohort studies[63-65] were identified regarding the clinical effectiveness and/or safety of MIGS versus comparators. The studies were published between 2004[61] and 2018[59] (Figure 1 identifies the number of publications by study year). The length of follow-up was at least 12 months in all but one study,[25] in which patients were followed for six months. The longest follow-up time point was 24 months in four studies,[58,63,64,90] 30 months in one study,[64] 36 months in one study,[58] and 42 months in one study.[59] In one study, the median follow-up duration was reported as 15.0 months in one group and 17.8 months in the other.[65]

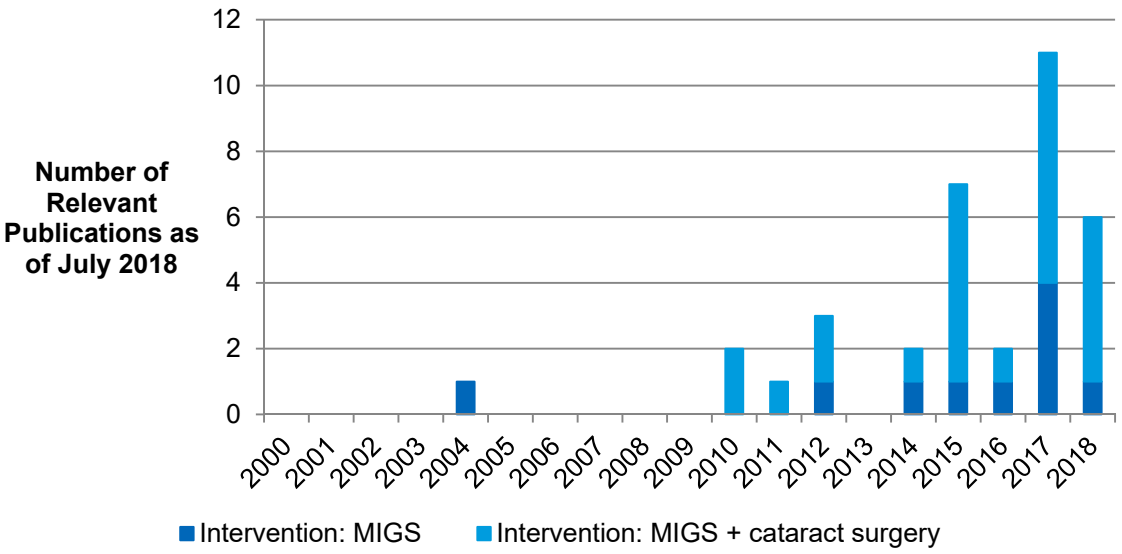
Authors of four studies (in five publications) received study funding from industry,[36,58-60,65] and authors of five studies reported no study funding or did not declare a source of funding.[25,61-64] Study authors reported several disclosures, including financial or non-financial support from industry, other involvement with industry (e.g., consulting for, or employee of, industry), or having other interests in manufacturer companies (e.g., shareholder, stockholder, or patent holders); complete details on author disclosures are reported in Table 30, Appendix 11.

MIGS in Combination With Cataract Surgery Versus Comparators (Research Questions 3 and 4):

Seven RCTs (in nine publications),[34,66-71,87,88] one non-randomized controlled clinical trial,[83] one prospective cohort study,[84] 13 retrospective cohort studies,[72-82,86,89] and one prospective and retrospective cohort study[85] were identified regarding the clinical effectiveness and/or safety of MIGS in combination with cataract surgery versus comparators. The studies were published between 2010[67,69] and 2018 (Figure 1).[85-89] The length of follow-up was at least 12 months in all but three studies,[76,82,86] in which patients were followed for six months. The longest follow-up time point was 12 months in nine studies,[69,73,77-81,83,87] 24 months in five studies,[68,70,71,88,89] 36 months in three studies,[75,84,85] and 48 months in one study.[66] In one study, the mean follow-up duration was 21 months (but was as little as two weeks),[72] and in another the mean follow-up duration was 2.1 months in one group (Phaco alone) and 7.4 months in the other (ECP + Phaco).[74]

Authors of six studies (in seven publications) received study funding from industry,[34,68-71,78,86] authors of 15 studies (in 16 publications) reported no study funding or did not declare a source of funding,[66,67,72-77,79-84,88,89] authors of one study reported funding from "The Japan Society for the Promotion of Science KAKENHI Grant,"[85] and one study's authors reported funding from the Faculty of Medicine and Dentistry at the University of Alberta.[87] Complete details on author disclosures are reported in Table 30, Appendix 11.

Figure 1: Number of Included Publications by Publication Year



MIGS = minimally invasive glaucoma surgery.

Note: Some publications reported on the same study.

Country of Origin

MIGS Versus Comparators (Research Questions 1 and 2)

The RCTs were conducted in Armenia,[58-60] or at multiple centres in Italy, Spain, Poland, Germany, and the UK.[36] The non-randomized controlled clinical trial was conducted in Brazil,[61] and the prospective cohort studies were conducted in Italy[62] and Germany.[25] The

retrospective cohort studies were conducted in the US,[63,64] or Austria, Belgium, Canada, and Germany.[65]

MIGS in Combination With Cataract Surgery Versus Comparators (Research Questions 3 and 4)

The RCTs were conducted in Canada,[87] Italy,[66,67] Spain,[69] the US,[34,68,70] or at multiple centres in Germany, Italy, Spain, and the Netherlands,[71] or Canada, Germany, Italy, Mexico, Philippines, Poland, Spain, the UK, and the US.[88] The non-randomized controlled clinical trial was conducted in Canada[83] and the prospective cohort study was conducted in the US.[84] The retrospective cohort studies were conducted in Canada,[79,82] Germany,[77] Iran,[89] Switzerland,[76] the UK,[72,73] the US,[74,75,80,81] or at multiple centres in Canada and the US,[78] or US and Mexico,[86] and the prospective and retrospective cohort study was conducted in Japan.[85]

Patient Population

MIGS Versus Comparators (Research Questions 1 and 2)

Mean patient age ranged from approximately 54[61] to 73[25] years across studies, and men and women were equally represented overall. Race was not reported in two studies,[62,63] but in all others the majority of patients were white.

All studies included patients with OAG,[25,36,58-65] and four studies included additional types of glaucoma. One retrospective cohort study also included patients with chronic angle-closure glaucoma (approximately 21%), secondary (30%), juvenile onset (4%), and congenital (3%) glaucoma,[63] and another retrospective cohort study also included patients with pseudoexfoliative glaucoma (approximately 13%), pigment dispersion syndrome (7%), and pigmentary (7%) or uveitic (5%) glaucoma.[64] A third retrospective cohort study also included patients with pseudoexfoliative (approximately 23%), pigment dispersion (6%), combined mechanism (6%), normal tension (2%), juvenile (3%), primary angle closure, (1%) or other (2%) glaucoma.[65] One non-randomized controlled clinical trial included patients with glaucoma classified as neovasular (approximately 40%), pseudophakic (29%), associated with penetrating keratoplasty (27%) and associated with vitreo-retinal surgery (4%).[61] In one RCT, one patient with pseudoexfoliative glaucoma was also included.[59,60]

Only one study provided information on glaucoma severity (based on visual field [VF] mean deviation), and eyes with mild (approximately 47%), moderate (20%), and advanced (33%) glaucoma were included.[65] In one study, glaucoma severity was reported as mild or moderate ("based on structural or functional characteristics," p. 2314)[60] per the study protocol.[59,60] Glaucoma severity was not reported in the other seven studies.[25,36,58,61-64]

Across eight studies, mean baseline IOP ranged from approximately 19.1 mm Hg[25] to 28.1 mm Hg[64] in the intervention groups and 23.1 mm Hg[62] to 28.0 mm Hg[25] in the comparator groups. In the ninth study, baseline IOP was much higher; mean baseline IOP was 41.61 mm Hg in the intervention group and 41.32 mm Hg in the comparator group.[61] Only one study reported medicated (19.8 mm Hg to 20.4 mm Hg) and unmedicated (25.0 mm Hg to 25.1 mm Hg) IOP across three intervention groups (one, two, or three iStents).[59,60] One study reported median IOP, 24.0 mm Hg in both groups (range 19.0 mm Hg to 30.0 mm Hg in the intervention group and 19.0 mm Hg to 32.0 mm Hg in the comparator group).[65]

Baseline number of glaucoma medications was not reported in two studies.[36,65] Across six studies, the mean number of glaucoma medications at baseline ranged from 0[58] to 3.3[64] in the intervention groups and 0[58] to 3.5[61] in the comparator groups. One study reported the

median number of medications as three (range of zero to four) in the intervention group and four (range of zero to five) in the comparator group.[63]

The proportion of patients who had undergone previous ocular procedures was not reported in three studies (four publications).[25,59-61] One study included only patients with no previous ocular procedures,[58] one study included patients who had not previously underwent selective laser trabeculoplasty (SLT) but did not report other procedures,[36] and four studies included patients with the following previous procedures (values are approximate % of the total study sample): argon laser trabeculoplasty (ALT; 5.5%),[64] SLT (1.8%[62] or 23.0%[64]), both ALT and SLT (11.1%),[64] Baerveldt Glaucoma Implant (BGI; 100%),[63] laser peripheral iridotomy (9.3%),[65] cataract surgery (33.6%),[65] or laser trabeculoplasty (41.5%).[65]

Relevant comorbidities were not reported in five studies (six publications).[58-63] Four studies included patients with comorbidities, as follows: cataract (number not reported),[36] controlled hypertension (12.5%),[25] mild dysfibrinogenemia defect (1.1%),[25] atopic dermatitis (2.3%),[25] hypertension (38.7%),[64] and diabetes (15.6%[64] or 9.3%[65]).

Additional information on detailed patient characteristics, including VF and visual acuity (VA), where available, is reported in Appendix 10.

MIGS in Combination With Cataract Surgery Versus Comparators (Research Questions 3 and 4):

Mean patient age ranged from approximately 62[89] to 79[83] years across studies, and men and women were equally represented overall. Race was not reported in nine studies,[66,67,69,72,76,79-82,84] but in all but four studies (in which all patients were Japanese[85] Iranian,[89] or multiracial with no majority racial group[73,86]) the majority of patients were white.

All studies included patients with OAG.[34,66-89] Sixteen studies included patients with additional types of glaucoma, as follows: angle-closure glaucoma,[75,76,82,86] normal-tension glaucoma,[75,76,86] pigmentary glaucoma,[34,68,71,76,78,86] pseudoexfoliative glaucoma,[34,68,71,77-79,82,83,87,89] exfoliation glaucoma,[85,86] secondary OAG,[85] neovascular glaucoma,[82] uveitic glaucoma,[82] plateau iris,[82] ocular hypertension,[76] congenital,[86] mixed mechanism,[83] or other glaucoma.[75,86] In three studies, the types of glaucoma that were eligible were reported but the proportions of included patients with each type were not; in addition to OAG, these included ocular hypertension,[69] normal-tension glaucoma,[72] pseudoexfoliative,[72,80] and pigmentary glaucoma.[72,80]

Information on glaucoma severity was reported in 18 studies.[34,68-70,73-81,83,84,86-89,91] In one study, glaucoma severity was reported as “mild to moderate” (based on preoperative VF data),[34,68] and in eight studies, glaucoma severity was reported per-protocol as mild or moderate[70,74-76,84,88] or as any severity.[78,80] In these studies, the method of rating severity was not specified,[70,76,80,88] or was rated based on VF measurement,[74,84] optic nerve cupping,[84] or the presence of particular characteristics (i.e., one to three glaucoma medications, stable glaucomatous field loss, and cupping between 0.6 and 0.8).[75] In two studies, there were roughly equivalent proportions of patients with mild and moderate glaucoma (defined by ICD-9 codes 365.71 and 365.73[86] or glaucomatous cupping/optic nerve abnormalities[77]).[77,86] In five studies, patients with mild, moderate, or advanced glaucoma were included.[69,79,81,83,87,88] In these studies, the method of rating severity was not specified,[89] or was determined by glaucomatous disc features,[87] VF defects,[87] the Canadian Ophthalmological Society clinical practice guidelines,[79,83] the American Academy of Ophthalmology Preferred Practice Pattern guidelines,[81] or the staging system by Mills et al.[92] (with the conversion method of Zeyen[93]).[69] In one study, glaucoma severity was described

as “early stage” in one group and as “uncontrolled or with previous failed surgery” in the other (based on VF mean deviation).[73] Glaucoma severity was not reported in the remaining five studies.[66,67,71,72,82,85]

Across studies, mean baseline IOP ranged from approximately 17.0 mm Hg[76] to 24.4 mm Hg[72] in the intervention groups and 16.1 mm Hg[74] to 24.5 mm Hg[72] in the comparator groups. Three studies[34,68,71,88] reported medicated (range of 17.9 mm Hg to 18.9 mm Hg) and unmedicated (range of 25.2 mm Hg to 26.6 mm Hg) IOP at baseline across intervention and comparator groups.

All studies included values for the number of glaucoma medications at baseline. However, one study did not report on baseline medications in the control group,[72] two studies reported multiple discrepant values (medications and associated *P* values) throughout the publications,[72,75] and three studies did not report statistical comparisons for between-group differences.[72,77,81] Across remaining studies, the mean number of glaucoma medications at baseline ranged from 1.1[69] to 3.2[85] in the intervention groups and 0.4[74] to 3.2[85] in the comparator groups.

Previous ocular procedures were not reported in nine studies (ten publications).[34,68,75,76,78,80,81,84-86] Five studies (six publications) excluded patients with previous ocular procedures.[66,67,69,74,77,89] Eight studies included patients with previous ocular procedures, as follows (values are ranges across studies of approximate % of the total study sample): Trabeculectomy (5.7% to 11.1%),[72,73,82] laser trabeculoplasty (1.0%),[71] ALT (0.8% to 17.0%),[72,79,83,87] SLT (5.0% to 44.3%),[73,79,83,87,88] ALT and/or SLT (11.3%),[82] transscleral cyclodiode laser (0.8%),[72] needling (3.0%),[73] glaucoma drainage device (GDD) (3.0%),[73] laser peripheral iridotomy (20.8%),[82,83] transscleral cyclophotocoagulation (2.0%),[73] or tube (1.9%).[82] In one study, it was reported that patients with previous laser trabeculoplasty were eligible for inclusion, but the proportion of included patients who had undergone this procedure was not reported.[70]

All patients included in the studies relevant to questions 3 and 4 had comorbid cataracts.[34,66-82,84-88] Additional relevant comorbidities were not reported in 16 studies (17 publications).[66,67,69,71,72,74-76,78-81,84-86,88,89] One study[70] excluded patients with “clinically significant ocular pathologies” but did not report specifics. Another study[77] excluded patients with other ocular or systemic diseases. Three studies (four publications) included patients with comorbidities, as follows (values are approximate % of the total study sample): posterior vitreous detachment (18%),[34,68] dry eye (13%),[34,68] age-related macular degeneration (5.6% to 10.0%),[34,68,82,83] age-related macular degeneration scar (1.9%),[83] high myopia (3.8%),[83] suprasellar lesion (3.8%),[83] branch vein occlusion (1.9%),[83] diabetic retinopathy (1.9%),[83] proliferative diabetic retinopathy (3.8%),[82] optic nerve head drusen (1.9%),[83] retinal vein occlusion (5.7%),[82] uveitis (5.7%),[82] retinal detachment (1.9%),[82] asthma (5.7%),[82] diabetes mellitus (9.4%),[82] hypertension (24.5%),[82] cerebral vascular accident (1.9%),[82] or thyroid problem (1.9%).[82]

Appendix 10 includes additional information on patient characteristics.

3.2.3 Interventions and Comparators

Table 2 includes a list of specific interventions and comparators, and Appendix 8 provides further details. Table 3 contains details on the total number of eyes in each intervention and comparator condition across studies in this report.

MIGS Versus Comparators (Research Questions 1 and 2)

For research questions 1 and 2, the interventions were the following MIGS: one,[59,60] two,[58-60] or three iStents;[59,60] one or two[25,36] iStent Injects; Hydrus Microstent;[62] endoscopic cyclophotocoagulation (ECP);[61,63] Trabectome;[25,64] and the Xen45 Microstent.[65] Comparators were medications (travoprost [a prostaglandin F analog][58] or a combination of Latanoprost and timolol [a prostaglandin F analog and beta-blocker][36]); SLT;[62] different numbers of iStents;[59,60] GDDs (BGI 250 or 350[63] or Ahmed Glaucoma Implant[61] [AGI]); and Trabeculectomy with mitomycin C (MMC).[25,64,65]

MIGS in Combination With Cataract Surgery Versus Comparators (Research Questions 3 and 4)

For research questions 3 and 4, the interventions were the following MIGS in combination with cataract surgery: goniotomy with the Kahook Dual Blade (KDB);[86] ECP;[72-75,82,84,89] one,[34,66-68,76,78,80,86] two,[69,76,79,80,83] or three[83] iStents; two iStent Injects;[77] CyPass Micro-Stent;[70] Hydrus Microstent;[71,88] or Trabectome.[77-79,85,87,89] Comparators were cataract surgery alone;[34,66-76,84,88] different numbers of iStents in combination with cataract surgery;[76,80,83] Trabeculectomy in combination with cataract surgery with MMC;[82,87] or trabeculotomy in combination with cataract surgery.[85] One MIGS in combination with cataract surgery was compared with another MIGS in combination with cataract surgery in six studies: goniotomy with KDB + phacoemulsification (Phaco) versus iStent + Phaco,[86] Trabectome + micro-incision cataract surgery (MICS) versus two iStent Injects + MICS,[77] ECP + iStent + Phaco versus iStent + Phaco,[81] and Trabectome + Phaco versus one[78] or two[79] iStents + Phaco, and ECP + Phaco versus Trabectome + Phaco.[89] The type of cataract surgery was phacoemulsification in all but one study, in which MICS was employed.[77]

Table 2: Interventions and Comparators in Included Studies

Intervention	Comparator	Studies
Research Questions 1 and 2		
MIGS Vs. Pharmacotherapy		
2x iStent	Travoprost (prostaglandin F analog)	Vold et al. 2016[58]
2x iStent Inject	Combination Latanoprost/timolol (prostaglandin F analog and beta-blocker)	Fea et al. 2014[36]
MIGS Vs. Laser Therapy		
Hydrus Microstent	SLT	Fea et al. 2017[62]
MIGS Vs. Another MIGS		
iStent vs. 2x iStent vs. 3x iStent	See column 1 for comparators	Katz et al. 2018[59] and 2015[60]
MIGS Vs. Filtration Surgery		
ECP	Second GDD (BGI)	Murakami et al. 2017[63]
ECP	AGI	Lima et al. 2004[61]
Trabectome	Trabeculectomy with MMC	Pahlitzsch et al. 2017[25] Jea et al. 2012[64]
2x iStent Inject	Trabeculectomy with MMC	Pahlitzsch et al. 2017[25]
Trabectome or 2x iStent Inject (grouped together)	Trabeculectomy with MMC	Pahlitzsch et al. 2017[25]
XEN 45 microstent with MMC	Trabeculectomy with MMC	Schlenker et al. 2017[65]
Research Questions 3 and 4		
MIGS + Cataract Surgery Vs. Cataract Surgery Alone		
ECP + Phaco	Phaco alone	Kang et al. 2017[72] Perez Bartolome et al. 2017[73] Sheybani et al. 2015[74] Siegel et al. 2015[75] Francis et al. 2014 [84]
iStent + Phaco	Phaco alone	Fea et al. 2015[66] Fea 2010[67] Craven et al. 2012[68] Samuelson et al. 2011[34] El Wardani et al. 2015[76]
2x iStent + Phaco	Phaco alone	El Wardani et al. 2015[76] Fernandez-Barrientos et al. 2010[69]
CyPass Micro-Stent + Phaco[a]	Phaco alone	Vold et al. 2016[70]
Hydrus Microstent + Phaco	Phaco alone	Pfeiffer et al. 2015[71] Samuelson et al. 2018[88]
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery		
KDB + Phaco vs. iStent + Phaco	See column 1 for comparators	Dorairaj et al. 2018[86]
Trabectome + Phaco vs. 2x iStent + Phaco	See column 1 for comparators	Kurji et al. 2017[79] Khan et al. 2015[78]
Trabectome + MICS vs. 2x iStent Inject + MICS	See column 1 for comparators	Gonnermann et al. 2017[77]
iStent + Phaco vs. 2x iStent+Phaco vs. 3x iStent + Phaco	See column 1 for comparators	Vlasov and Kim 2017[80] Belovay et al. 2012[83]
ECP + iStent + Phaco vs. iStent + Phaco	See column 1 for comparators	Ferguson et al. 2017[81]

Intervention	Comparator	Studies
ECP + Phaco vs. Trabectome + Phaco	See column 1 for comparators	Moghimi et al. 2018[89]
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery		
Trabectome + Phaco	Trabeculectomy with MMC + Phaco	Ting et al. 2018[87]
Trabectome + Phaco	Trabeculotomy + Phaco	Kinoshita-Nakano et al. 2018[85]
ECP + Phaco	Trabeculectomy with MMC + Phaco	Marco et al. 2017[82]

2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; BGI = Baerveldt glaucoma implant 250 or 350; ECP = endoscopic cyclophotocoagulation; GDD = glaucoma drainage device; KDB = Kahook Dual Blade; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; Phaco = phacoemulsification; SLT = selective laser trabeculoplasty; vs. = versus.

[a] The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the Medical Devices Active Licence Listing and is therefore included in this report.

Table 3: Number of Eyes for Each Intervention and Comparator

Intervention or Comparator	Number of Eyes	Intervention or Comparator	Number of Eyes
Research Questions 1 and 2:		**Research Questions 3 and 4:**	
Interventions			
Hydrus Microstent	31	Trabectome + MICS	25
iStent	38	2x iStent Inject + MICS	25
3x iStent	40	3x iStent + Phaco	25
Travoprost	47	ECP + iStent + Phaco	51
ECP	59	Trabectome + Phaco	171
2x iStent	95	2x iStent + Phaco	180
Latanoprost and Timolol	98	KDB + Phaco	237
2x iStent Inject	114	CyPass Micro-Stent + Phaco[a]	374
Trabectome	158	Hydrus Microstent + Phaco	419
Xen45 with MMC	185	iStent + Phaco	447
		ECP + Phaco	614
Intervention total	**865**	**Intervention total**	**2,568**
Comparators			
SLT	25	Trabeculotomy + Phaco	29
AGI	34	Trabeculectomy with MMC + Phaco	38
BGI	48	Phaco alone	891
Trabeculectomy with MMC	296		
Comparator total	**403**	**Comparator total**	**958**
TOTAL for questions 1 and 2	*1,268*	***TOTAL for questions 3 and 4***	*3,526*
Total in intervention groups: 3,433 **Total in comparator groups: 1,361** **Grand total: 4,794**			

2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; BGI = Baerveldt glaucoma implant 250 or 350; ECP = endoscopic cyclophotocoagulation; KDB = Kahook Dual Blade; MICS = micro-incision cataract surgery; MMC = mitomycin C; Phaco = phacoemulsification; SLT = selective laser trabeculoplasty.

[a] The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the Medical Devices Active Licence Listing and is therefore included in this report.

3.2.4 Critical Appraisal of Individual Studies

A summary of the risk of bias assessment can be found in Table 4 for RCTs and Table 5 for all other study designs. Overall, each of the included studies exhibited some risk of bias.

Risk of Bias in Randomized Controlled Trials

All included RCTs used appropriate methods of randomization.[34,36,58-60,66-71,87,88] Only one RCT[87] explicitly reported allocation concealment; however, the inclusion criteria were changed after the start of the trial, which introduced risk of selection bias. No other RCTs explicitly reported allocation concealment;[34,36,58-60,66-71,88] therefore, all RCTs were at possible risk of selection bias.

There was a low risk of performance bias in nine of the 10 RCTs.[34,36,58,66-71,88] In two RCTs, adequate blinding of patients and outcome assessors was ensured,[66,67,70] and in seven RCTs there was no blinding but also no reasons to suspect systematic differences between groups in the care provided or in exposure to factors other than the intervention of interest.[34,36,58,68,69,71,88] In the final RCT, the study occurred over a long duration and how the intervention was conducted in one treatment arm (Trabectome) changed over the course of the study, leading to a risk of performance bias.[87]

Detection bias was assessed separately for individual outcomes. IOP was measured objectively by tonometry in nine RCTs;[34,58-60,66-71,87,88] the method of measurement was not reported in the tenth.[36] In four RCTs, diurnal variation in IOP was accounted for in its measurement, resulting in no risk of detection bias.[36,70,71,88] In the other six RCTs, either diurnal variation in IOP was not accounted for, or whether it was accounted for was unclear, resulting in a risk of detection bias.[34,58-60,66-69,87] There was an unclear risk of detection bias in the measurement of the number of glaucoma medications and in the measurement of AEs and complications in every RCT, because the methods of measurement were not reported in any study.[34,58-60,66-71,87,88] Similarly, for VF, there was a risk of detection bias in two of three RCTs.[34,58-60,68] In one study, the method of measuring VF was not specified,[59,60] and in the other there was no blinding of outcome assessors.[34,68] VA was reported in four RCTs,[34,36,58-60,68] and there was a risk of detection bias in three of these because the details of measurement were not reported.[34,36,59,60,68]

There was a low risk of attrition bias in eight RCTs up to at least 15 months of follow-up.[34,36,58-60,66-70,88] In two of these RCTs, there was a risk of attrition bias at later follow-up time points (36-month[58] or 4-year[66,67] follow-up) due to large amounts of missing data and/or an imbalance in the proportion of missing data across groups. In the remaining two RCTs there was a high risk of attrition bias due to large amounts of missing data,[58,66,67] and because the reasons for missing data may have been due to outcomes of interest (e.g., in one study,[34,68] those with failed phacoemulsification were excluded post-randomization).

There was a high risk of reporting bias in five RCTs.[34,36,58-60,68,87] In two studies, expected outcomes were reported in the results but statistical comparisons were not conducted or *P* values were not reported.[36,58] In one RCT, the results were not reported comprehensively and the rationale for the choice of analysis was not reported (i.e., some results were reported with the intention-to-treat population, and others with a “consistent cohort” population).[34,68] Additionally, 90% CIs were used and no rationale was provided; 90% CIs are not standard and may have been chosen to avoid crossing the line of no effect or to avoid overlap in CIs between groups.[34,68] In one RCT, outcomes that were specified a priori in a clinical trials registry (i.e., quality of life [QoL] and VA) were not included in the published

study.[87] In the final RCT, expected results were reported incompletely; for example, the absolute number of glaucoma medications was not reported, but rather only the proportion of patients on any medications.[59,60]

Finally, one RCT had an additional source of bias; the study was stopped early due to difficulties with recruitment and therefore enrolled fewer patients than planned a priori.[87] There were fewer than 10 studies for each intervention and comparator, so the risk of publication bias was considered non-evaluable.

Additional details regarding the risk of bias for studies contributing to individual comparisons are provided in the "risk of bias" components of the GRADE tables in Appendix 13.

Table 4: Risk of Bias Summary — Randomized Controlled Trials

	Selection Bias — Random Sequence Generation	Selection Bias — Allocation Concealment	Performance Bias	Detection Bias — IOP	Detection Bias — Number of Medications, Adverse Events, Other	Attrition Bias	Reporting Bias — Selective Reporting	Other Sources of Bias
Research Questions 1 and 2:								
Vold et al. 2016[58]	✓	?	✓	X	?	✓ / X[a]	X	✓
Fea et al. 2014[36]	✓	?	✓	✓	?	✓	X	✓
Katz et al. 2015[60] and Katz et al. 2018[59]	✓	?	✓	X	?	✓	X	✓
Research Questions 3 and 4:								
Samuelson et al. 2018[88]	✓	?	✓	✓	?	✓	✓	✓
Ting et al. 2018[87]	X	✓	X	X	?	X	X	X
Vold et al. 2016[70] [b]	✓	?	✓	✓	?	✓	✓	✓
Fea et al. 2015[66] and Fea 2010[67]	✓	?	✓	X	?	✓ / X[c]	✓	✓
Pfeiffer et al. 2015[71]	✓	?	✓	✓	?	✓	✓	✓
Craven et al. 2012[68] and Samuelson et al. 2011[34]	✓	?	✓	X	?	X	X	✓
Fernandez-Barrientos et al. 2010[69]	✓	?	✓	X	?	✓	✓	✓

✓ = low risk of bias; ? = unclear risk of bias; X = high risk of bias; IOP = intraocular pressure.

[a] Low risk of bias at 12- and 24-month follow-up; high risk of bias at 36-month follow-up.

[b] In this study, the CyPass Micro-Stent in combination with cataract surgery was compared with cataract surgery alone. The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the Medical Devices Active Licence Listing and is therefore included in this report.

[c] Low risk of bias up to 15 months of follow-up; high risk of bias at four-year follow-up.

Risk of Bias in Other Study Designs

Among the 22 studies of other designs, bias due to confounding was considered low in one,[77] moderate in four,[25,65,78,85] serious in 16,[25,62-64,72,74-76,79-84,86,89] and critical in one study.[73] There was deemed a risk of bias due to confounding when significant differences between groups at baseline were not controlled;[62,64,65,73,74,79,81,82,84,89] different surgeons performed the interventions in different treatment groups;[63,79] pseudorandomization was employed;[61] potential confounding variables were not controlled for in analyses;[25,61,63-65,72-76,78-81,83-86,89] treatment was selected based on patient characteristics, patient choice, and/or it was a retrospective study and the rationale for assigning treatments was likely different between groups;[25,64,72-76,78-81,83,86,89] baseline characteristics were not reported for one group so it was not possible to assess whether groups were systematically different at baseline;[72] how patients were prospectively assigned to groups was not reported;[84] or data were collected prospectively for one group and retrospectively for the other and it was possible that the groups were systematically different.[85]

Bias in the selection of participants was considered low in nine studies,[25,61,62,64,75,76,80-82] moderate in 10 studies,[63,65,73,77-79,83-86] serious in one study,[72] and critical in two studies.[74,89] A risk of bias in the selection of participants was considered when only patients with a given follow-up duration and/or complete data were included (and were potentially systematically different from those in routine clinical practice who may have had a shorter follow-up duration or missing data),[63,65,72,73,77-79,83-86,89] patients with intraoperative complications were excluded,[74] or at least one patient who did not meet inclusion criteria was included (the inclusion criteria specified age > 40 years, but the range of ages in one group was reported as 30 to 85 years).[89]

Bias in classification of interventions was considered low in all studies because the interventions were classified or defined based on the treatments received.

Bias due to deviations from intended interventions was considered low in seven studies,[61-63,65,79,80,89] moderate in one study,[77] serious in 13 studies,[25,64,72,73,75,76,78,81-86] and critical in one study.[74] Bias due to deviations from intended interventions was considered serious when the post-intervention medication regimen (i.e., a co-intervention) was different across treatment arms[72,73,76,77] and/or in cases where the number of medications was reported and was significantly different between treatment arms.[25,64,74,75,78,81-86] In one study, this was the case only at one of the follow-up time points (six weeks) and therefore bias due to deviations from intended interventions was deemed moderate.[77] Bias due to deviations from intended interventions was considered critical in one study because, in addition to an imbalance in an important co-intervention (i.e., medications) across groups, it was unclear whether the intervention was implemented successfully for most participants (i.e., patients who experienced intraoperative complications were excluded, and the proportion of patients affected was not reported).[74]

Bias due to missing data was considered low in nine studies,[25,62,73,75,77,79,81,83,89] moderate in one study,[86] serious in ten studies,[61,63-65,74,76,78,80,82,85] and critical in one study.[72] In one study, the risk of bias due to missing data was considered low up to 24 months of follow-up and serious for later follow-up time points.[84] There was deemed a risk of bias due to missing data when there was substantial loss to follow-up,[61,63,64,76,78,80,82,84-86] the amount of missing data was not balanced across groups,[61,63,76,78,80,82,85,86] reasons for missing data were not reported,[61,63,64,76,80,82,84-86] and/or no information on the amount or nature of missing data was reported.[65] Bias due to missing data was considered critical in one study because data were not reported at baseline or follow-up for some variables for the comparator group.[72]

QoL was only measured in one prospective cohort study,[25] and bias in its measurement was considered serious because although it was measured using a validated questionnaire (the National Eye Institute Visual Functioning Questionnaire – 25 [NEI VFQ-25])[95] this tool did not include reliance on medications which would be expected to impact QoL.

Bias in measurement of IOP was considered low in one study[61] and serious in all others.[25,62-65,72-86,89] The risk of bias in measurement of IOP was considered low in one study because IOP was always measured at the same time of day, which accounted for diurnal variation.[61] In all other studies, bias in measurement of IOP was considered serious because diurnal variation in IOP was not accounted for,[25,62-65,72-76,84,86] or whether it was accounted for was unclear,[77-83,85,89] or because IOP was measured without medication washout and the number of medications was significantly different between groups[25,63,64,74-78,81-86] (or was not evaluable because it was not reported in the comparator group,[72] or not compared statistically between groups[73]).

Bias in measurement of number of medications was considered serious in all studies because the method of measurement was not specified.[25,61-65,72-86,89]

VA was reported in 15 studies.[25,61,62,64,65,72-77,79,82,83,86] Bias in measurement of VA was considered serious in all cases because the method of measuring VA was not reported,[25,62,64,76,77] was not reported in sufficient detail to establish validity and reliability,[61] or was reported to be measured using a method known[96] to have poor validity or reliability.[65,72-75,79,82,83,86]

Bias in measurement of safety parameters (i.e., AEs and complications) was considered serious in all studies because the methods of measurement were not reported. [25,61-65,72-86,89] In addition, whether there was any restriction on what was considered an AE or complication was not reported. Therefore, if no detail on a particular AE was reported in a given study it is unclear whether this was because the particular AE did not occur or whether information on that AE was not collected.

Bias in selection of the reported result was considered low in eight studies because all results were reported as specified in the methods.[73,74,77,78,80,82,83,85] Bias in selection of the reported result was considered moderate in six studies[63-65,79,84,89] because some preoperative population characteristics that were measured were not reported,[63] VA was only reported at a subset of measured time points,[64] VF was not included in the methods as an outcome measure but was included as such in the results,[89] no rationale was provided for reporting findings as medians instead of means and absolute values for IOP were reported only at “last follow-up,”[65] there was inconsistency in reporting of AEs between the abstract and main text,[79] and the types of analyses were not described in the methods and reductions from baseline were presented only as proportions for IOP but as absolute values for other outcomes and no rationale was provided.[84] Bias in selection of the reported result was considered serious in six studies[25,61,62,75,81,86] because some relevant statistical comparisons were not conducted or reported;[62] some variables were only reported at a subset of the time points at which they were measured;[61,62] a composite measure of QoL that was described in the methods was not reported in the results;[25] values for VA were only reported pooled across treatment groups, no measures of variability were included for the primary outcome variable, and between-group statistical comparisons were not reported at baseline;[86] VA was measured at all time points but not reported as an outcome;[81] and there was inconsistent reporting such that the between-group difference in number of medications at baseline was reported to be statistically significant or non-significant in two different tables.[75] Bias in selection of the reported result was considered critical in two studies[72,76]

because key data for the comparator group were not reported at baseline or follow-up time points[72] and because there was inconsistent reporting (i.e., different values reported in abstract, tables, and text) so interpretation of findings was unclear.[76]

There were fewer than 10 studies for each intervention and comparator, so the risk of publication bias was considered non-evaluable.

Additional details regarding the risk of bias for studies contributing to individual comparisons are provided in the "risk of bias" components of the GRADE tables in Appendix 13.

Table 5: Risk of Bias Summary — Other Study Designs

	Bias Due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations From Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result
Research Questions 1 and 2:							
Fea et al. 2017[62]	S	L	L	L	L	S	S
Murakami et al. 2017[63]	S	M	L	L	S	S	M
Lima et al. 2004[61]	M	L	L	L	S	M	S
Pahlitzsch et al. 2017[25]	S	L	L	S	L	S	S
Jea et al. 2012[64]	S	L	L	S	S	S	M
Schlenker et al. 2017[65]	M	M	L	L	S	S	M
Research Questions 3 and 4:							
Dorairaj et al. 2018[86]	S	M	L	S	M	S	S
Kinoshita-Nakano et al. 2018[85]	M	M	L	S	S	S	L
Moghimi et al. 2018[89]	S	C	L	L	L	S	M
Ferguson et al. 2017[81]	S	L	L	S	L	S	S
Gonnermann et al. 2017[77]	L	M	L	M	L	S	L
Kang et al. 2017[72]	S	S	L	S	C	S	C
Kurji et al. 2017[79]	S	M	L	L	L	S	M
Marco et al. 2017[82]	S	L	L	S	S	S	L
Perez Bartolome et al. 2017[73]	C	M	L	S	L	S	L
Vlasov and Kim 2017[80]	S	L	L	L	S	S	L
El Wardani et al. 2015[76]	S	L	L	S	S	S	C
Khan et al. 2015[78]	M	M	L	S	S	S	L
Sheybani et al. 2015[74]	S	C	L	C	S	S	L

	Bias Due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations From Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result
Siegel et al. 2015[75]	S	L	L	S	L	S	S
Francis et al. 2014[84]	S	M	L	S	L/S[a]	S	M
Belovay et al. 2012 [83]	S	M	L	S	L	S	L

L = low; M = moderate; S = serious; C = critical.

Note: In some cases, ratings for risk of bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result differed across outcomes within a given study (e.g., "moderate" for bias in measurement of intraocular pressure, but "serious" for bias in measurement of number of medications). In these instances, the least favourable (i.e., most severe) rating was included in this table.

[a] Low risk of bias for up to 24-months of follow-up; serious risk of bias for later time points.

Quality Assessment: Overall Body of Evidence

The quality of evidence for each outcome by each comparison and study design is presented in GRADE evidence profile tables in Appendix 13. Overall, the quality of evidence ranged from "very low" to "high." The most common reasons for downgrading the quality of the evidence were: 1) serious risk of bias that reduced the level of confidence in the observed effects (as described in the "Quality Assessment: Individual Studies" section), 2) and serious imprecision (e.g., only a single study for a given comparison, no measures of variability, or wide variability leading to uncertainty about the true magnitude of the effect).

For AEs and harms outcomes, the quality of the evidence for all groupings of studies (i.e., by intervention and comparison, and study design) was also downgraded for "serious indirectness" because the method of measuring AEs or harms was not specified; therefore, it was not possible to determine whether direct or surrogate measures were used, or whether data on all patient-important AEs or harms were collected. Similarly, all groupings of studies were considered to have "serious imprecision" because there were relatively few AEs or harms and no measures of variability, leading to uncertainty about the true between-group differences. Judgments for "inconsistency" were largely subjective given that most studies did not conduct statistical comparisons for between-group differences in the incidence of AEs or harms, and/or had too few events to accurately evaluate heterogeneity. Overall, the quality of the evidence for AEs and harms outcomes was "very low."

3.2.5 Outcomes

A complete list of included outcomes and their measures (where reported) can be found in Appendix 8.

Only one study included the primary outcome of interest, a measure of QoL (measured by the NEI VFQ-25).[25] This measure included 12 subscales (i.e., general health, ocular pain, general vision, near activities, distance activities, mental health, social functioning, role difficulties, dependency, driving, colour vision, and peripheral vision).

All studies included IOP, measured by Goldmann applanation tonometry (where the method of measurement was reported), as an outcome (absolute IOP, absolute or relative change in IOP, and/or the proportion of eyes achieving a given target IOP). Appendix 9 includes information on the validity of IOP as a surrogate end point.

The number of glaucoma medications (or proportion of eyes requiring glaucoma medications) was an outcome in all studies except for the two in which pharmacotherapy was the comparator.[36,58] The method of measuring number of glaucoma medications was not reported in any study.

VF was an outcome in two studies (three publications) for Research Question 1,[58-60] and in two studies (three publications) for Research Question 3.[34,68,89] VF was measured by Humphrey 24-2 or 30-2 Swedish Interactive Threshold Algorithm in all cases but one,[59,60] in which the method of measurement was not reported.

VA outcomes were included in eight studies (in nine publications) for Research Question 1 (VA[25,61,62,64] or best-corrected visual acuity [BCVA][36,58-60,65]), and in 11 studies (12 publications) for Research Question 3 (VA,[72,73,75,76,82] BCVA,[74,77,79,86] or corrected-distance visual acuity [CDVA][34,68,83]). The method of VA measurement was not reported in five studies (seven publications).[25,34,36,59,60,68,76] In other studies, VA was measured using Snellen,[72-75,79,83] Snellen converted to logarithm of the minimum angle of resolution (logMAR),[65,82,86] or decimal chart.[58] In four studies, VA was reported in logMAR but the original method of measuring VA was not reported.[61,62,64,77]

For research questions 2 and 4, safety outcomes were intraoperative or post-operative AEs and complications, and were reported in all but four studies.[25,74,76,85] The method of measuring AEs and complications was not reported in any study. Similarly, whether there was any restriction on what was considered an AE or complication was not reported. Therefore, if no detail on a particular AE was reported in a given study, it is unclear whether this is because the particular AE did not occur or whether information on that AE was not collected. Nine studies also provided information on requirement for secondary procedures.[63-65,75,81,86-89]

Detailed outcome data are reported in Appendix 12.

3.2.6 Data Analysis and Synthesis

A detailed summary of study findings is provided in Appendix 12 by study, and in Appendix 13 by outcome along with the GRADE quality assessments. A high-level summary of study findings by comparison and outcome is presented in Table 6. Note that Table 6 presents findings for each overarching category (e.g., MIGS versus pharmacotherapy), and each individual comparison within each category (e.g., which particular MIGS versus which particular pharmacotherapy) in terms of the direction of effect for each outcome (e.g., not significantly different between groups, or more or less favourable in MIGS versus comparators); additional detail is provided in the table footnote.

Unless otherwise stated, there were no between-group differences at baseline (i.e., pre-intervention). All data presented are unadjusted (i.e., not adjusted for covariates).

Table 6: High-Level Summary of Findings by Comparison and Outcome

Overarching Category	Comparison	Direction of Effect by Outcome					
	Intervention Vs. Comparator	IOP	# meds	QoL	VF	VA	Safety
Research Questions 1 and 2: MIGS Vs. Comparators							
MIGS vs. pharmacotherapy	2x iStent vs. Travoprost,[58] or 2x iStent Inject vs. Latanoprost + Timolol[36]	**[?]**	**NA**	–	**[?]**	**[?]**	**[?]**
MIGS vs. laser therapy	Hydrus Microstent vs. SLT[62]	**NS**	**>**	–	–	**[?]**	**[?]**
MIGS vs. another MIGS	1 vs. 2 vs. 3 iStent(s)[59,60]	**1 < 2 < 3**	**1 [?] 2 [?] 3**	–	**1 NS 2 NS 3**	**1 [?] 2 [?] 3**	**1 [?] 2 [?] 3**
MIGS vs. filtration surgery	ECP vs. GDD (BGI or AGI)[61,63]	**NS**	**NS**	–	–	**NS**	**NS / >**
	Trabectome vs. Trabeculectomy with MMC[25,64]	**[?] / <**	**<**	**> / NS**	–	**[?]**	**< / >**
	2x iStent Inject vs. Trabeculectomy with MMC[25]	**[?]**	**[?]**	**NS**	–	**[?]**	–
	Trabectome or 2x iStent Inject (grouped together) vs. Trabeculectomy with MMC[25]	**NS**	**<**	**NS**	–	**NS**	–
	Xen45 with MMC vs. Trabeculectomy with MMC[65]	**NS**	**[?]**	–	–	**NS**	**[?]/NS**
Research Questions 3 and 4: MIGS + Cataract Surgery Vs. Comparators							
MIGS + cataract surgery vs. cataract surgery alone	ECP + Phaco vs. Phaco alone[72-75,84]	**NS / >/ [?]**	**[?]**	–	–	**= / [?]**	**[?] / <**
	iStent + Phaco vs. Phaco alone[34,66-68,76]	**NS**	**NS**	–	**NS**	**[?]**	**[?]**
	2x iStent + Phaco vs. Phaco alone[69,76]	**> / [?]**	**>/[?]**	–	–	–	**[?]**
	CyPass Micro-Stent + Phaco vs. Phaco alone[70 a]	**>**	**>**	–	–	–	**NS / >**
	Hydrus Microstent + Phaco vs. Phaco alone[71,88]	**>**	**>**	–	–	–	**NS / <**
MIGS + cataract surgery vs. a different MIGS + cataract surgery	Goniotomy with KDB + Phaco vs. iStent + Phaco[86]	**>**	**>**	–	–	**NS**	**NS / >**
	Trabectome + Phaco vs. 2x iStent + Phaco[78,79]	**< / [?]**	**NS**	–	–	**NS**	**< / NS**
	Trabectome + MICS vs. 2x iStent Inject + MICS[77]	**NS**	**NS**	–	–	**NS**	**[?]**
	Different numbers of iStents + Phaco[80,83]	**1 NS 2 NS 3**	**1 NS 2 < 3**	–	–	**2 [?] 3**	**[?]**
	ECP + iStent + Phaco vs. iStent + Phaco[81]	**>**	**<**	–	–	–	**[?]**
	ECP + Phaco vs. Trabectome + Phaco[89]	**NS**	**NS**	–	NS	–	**[?]**
MIGS + cataract surgery vs. filtration surgery + cataract surgery	Trabectome + Phaco vs. Trabeculectomy with MMC + Phaco[87]	**NS**	**NS**	–	–	–	**NS**
	Trabectome + Phaco vs. Trabeculotomy + Phaco[85]	**NS**	**NS**	–	–	–	–
	ECP + Phaco vs. Trabeculectomy with MMC + Phaco[82]	**NS**	**<**	–	–	**NS**	**< / [?]**

> = intervention more favourable than comparator; < = intervention less favourable than comparator; [?] = not compared statistically or non-interpretable; – = not measured; 2x = two devices; AGI = Ahmed glaucoma implant; BGI = Baerveldt glaucoma implant; ECP = endoscopic cyclophotocoagulation; GDD = glaucoma drainage device; IOP = intraocular pressure; KDB = Kahook Dual Blade; meds = medications; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; NA = not applicable; NS = not significantly different between groups; Phaco = phacoemulsification; QoL = quality of life; Safety = safety outcomes grouped together (i.e., adverse events and complications); SLT = selective laser trabeculoplasty; VA = visual acuity; VF = visual field; vs. = versus.

Note: If findings were different at incremental follow-up time points, the longest available follow-up time point was used in describing the overall findings. More than one symbol for a given comparison indicates mixed findings, with results differing within or across studies.

[a] The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the Medical Devices Active Licence Listing and is therefore included in this report.

Research Question 1: What is the comparative clinical effectiveness of MIGS versus each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?

Quality of Life

A detailed summary of findings is provided in the GRADE evidence profile table (Table 7). GRADE tables for all other outcomes are presented in Appendix 13.

MIGS Versus Filtration Surgery

MIGS (Trabectome or Two iStent Injects) Versus Trabeculectomy With MMC

QoL was assessed (using the National Eye Institute Visual Functioning Questionnaire - 25) in a single prospective cohort study that compared the effect of MIGS (either Trabectome or two iStent Injects, examined separately or grouped together) with Trabeculectomy with MMC.[25] In brief, only one out of 12 QoL parameters (colour vision) was significantly greater in the Trabectome versus Trabeculectomy group at six-month follow-up (mean between-group difference of approximately 13 points on a 100-point scale); all other parameters were not significantly different between groups.[25] None of the 12 QoL parameters were significantly different between the two iStent Injects and Trabeculectomy groups, or between the MIGS and Trabeculectomy groups, at six-month follow-up.[25] QoL was not reported at baseline.[25]

Intraocular Pressure

A detailed summary of findings is provided in Table 32 and Table 33, Appendix 13. IOP was measured without medication washout unless otherwise stated.

MIGS Versus Pharmacotherapy

Two iStents Versus Travoprost, or Two iStent Injects Versus Latanoprost + Timolol

In two RCTs, there was a numerical reduction in IOP from baseline at 1 to 36 months following two iStents or Travoprost (reduction of approximately 10 mm Hg),[58] or at 1 to 12 months following two iStent Injects or Latanoprost + Timolol (reduction of approximately 8 mm Hg),[36] but differences within or between groups were not tested statistically.[36,58] A significantly greater proportion of eyes in the two iStent Injects (53.2%) group versus the Latanoprost + Timolol (35.7%) group achieved a ≥ 50% IOP reduction from baseline at 12-month follow-up, but there was no difference between groups in the proportion of eyes that achieved a ≥ 20%, 30%, or 40% IOP reduction from baseline.[36] The proportion of eyes achieving absolute IOP ≤ 15 mm Hg or ≤ 18 mm Hg was reported in both studies, but between-group differences were not tested statistically.[36,58]

MIGS Versus Laser Therapy

Hydrus Microstent Versus SLT

In a single prospective cohort study, IOP was significantly reduced from baseline at 1 to 12 months following Hydrus Microstent or SLT (reduction of approximately 4 mm HG to 7 mm Hg), but was not significantly different between groups at any time point.[62] There was no difference between groups in the proportion of eyes achieving a >20% reduction in IOP from baseline at 12 month follow-up.[62]

Table 7: Effect of MIGS Versus Comparators on Quality of Life in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS Vs. Filtration Surgery: Trabectome Vs. Trabeculectomy With MMC											
1	Prospective cohort[a]	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	None	43	25	**Mixed Findings; Trabectome >/= Trabeculectomy with MMC:** Only 1/12 QoL parameters (colour vision) was significantly greater in the *Trabectome* vs. *Trabeculectomy* group at 6 mo follow-up; all other parameters were not significantly different between groups.[25]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: 2x iStent Inject Vs. Trabeculectomy With MMC											
1	Prospective cohort[a]	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	None	20	25	**2x iStent Inject = Trabeculectomy with MMC:** None of the 12 QoL parameters were significantly different between the *2x iStent Inject* vs. *Trabeculectomy* groups at 6 mo follow-up.[25]	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS Vs. Filtration Surgery: Trabectome or 2x iStent Inject Vs. Trabeculectomy With MMC											
1	Prospective cohort[a]	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	None	63	25	**MIGS = Trabeculectomy with MMC:** None of the 12 QoL parameters were significantly different between the *MIGS* (combined *Trabectome* and *2x iStent Inject*) vs. *Trabeculectomy* groups at 6 mo follow-up.[25]	⊕OOO VERY LOW	CRITICAL

= = not significantly different between groups; > = intervention more favourable than comparator; 2x = two devices; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = months; no. = number; QoL = quality of life; vs. = versus.

Note: Data were collected by prospective cohort, with up to six months of follow-up. Quality of life was measured using 12 subscales (general health, ocular pain, general vision, near activities, distance activities, mental health, social functioning, role difficulties, dependency, driving, colour vision, peripheral vision) and overall composite (that included all but the general health subscale) of the National Eye Institute-Visual Functioning Questionnaire.:.

[a] One prospective cohort study.[25]

[b] Serious risk of bias.[25] Bias due to confounding: decision for MIGS versus Trabeculectomy was made by treating surgeon based on patient characteristics, and choice of MIGS was made by individual patients; potential confounding variables not controlled for in analyses. Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias in measurement of outcomes: the tool used to assess quality of life did not include reliance on medications, which would be expected to impact quality of life. Bias in selection of the reported result: results for the "composite" measure of quality of life not reported in the results.

[c] Serious imprecision.[25] Only a single study.[25]

MIGS Versus Another MIGS

One Versus Two Versus Three iStent(s)

In a single RCT, IOP was significantly reduced from baseline at 18 months of follow-up in eyes with one, two, or three iStents, and the reduction was incrementally greater with increasing numbers of iStents (reductions of approximately 4 mm Hg, 6 mm Hg, and 8 mm Hg after medication washout for one, two, and three iStents respectively).[59,60] Although IOP was measured at up to 42 months of follow-up, between-group differences were not compared statistically at other time points. Similarly, the between-group differences in the proportion of eyes achieving a ≥ 20% reduction in IOP from baseline, or an absolute IOP of ≤ 15 mm Hg or ≤ 18 mm Hg, were not compared statistically.[59,60]

MIGS Versus Filtration Surgery

ECP Versus Glaucoma Drainage Device

In a retrospective cohort study, IOP was significantly reduced from baseline (by approximately 7 mm Hg to 11 mm Hg) in both ECP and BGI groups at 3 to 24 months of follow-up, but was not significantly different between groups at any time point.[63]

In a non-randomized controlled clinical trial, IOP was significantly reduced from baseline (by approximately 19 mm Hg to 36 mm Hg) in both ECP and AGI groups from one week to 24 months of follow-up (only tested statistically at 24 months).[61] The reduction in IOP was significantly greater in AGI versus ECP at the one-week follow-up, in ECP versus AGI at the two-, three-, and four-month follow-ups, and was not significantly different between groups thereafter up to 24 months of follow-up.[61] There was no significant difference between groups in the proportion of patients with IOP > 6 mm Hg and < 21 mm Hg at 24 months of follow-up.[61]

Trabectome Versus Trabeculectomy With MMC

In a prospective cohort study, IOP was significantly reduced from baseline (a reduction of approximately 4 mm Hg to 15 mm Hg) in both the Trabectome and Trabeculectomy groups at six months of follow-up (to approximately 14.7 mm Hg and 12.9 mm Hg, respectively), but between-group differences were not tested statistically.[25] In a retrospective cohort study, IOP was not different between groups at baseline, was numerically reduced from baseline in both groups (not tested statistically), and was significantly higher in the Trabectome versus Trabeculectomy group at all follow-up time points (1 to 30 months; at 30 months IOP was approximately 16.6 mm Hg and 10.0 mm Hg respectively).[64]

Two iStent Injects Versus Trabeculectomy With MMC

In a prospective cohort study, IOP was significantly reduced from baseline (by approximately 5 mm Hg to 15 mm Hg) in both the two iStent Injects and Trabeculectomy groups at the six-month follow-up (to approximately 16.0 mm Hg and 12.9 mm Hg, respectively), but between-group differences were not tested statistically.[25]

Trabectome or Two iStent Injects Versus Trabeculectomy With MMC

In a prospective cohort study, eyes that received Trabectome or two iStent Injects were grouped together as “MIGS.”[25] IOP was significantly higher in the MIGS versus Trabeculectomy group at six-week and three-month follow-up (by approximately 2 mm Hg to 32 mm Hg), but there was no significant difference between groups at the six-month follow-up.[25]

Xen45 With MMC Versus Trabeculectomy With MMC

In a retrospective cohort study, IOP was not significantly different between the Xen45 and Trabeculectomy groups at baseline or follow-up (a median follow-up duration of 15.0 and 17.8 months respectively).[65]

Number of Glaucoma Medications

A detailed summary of findings is provided in Table 34, Appendix 13.

MIGS Versus Laser Therapy

Hydrus Microstent Versus SLT

In a single prospective cohort study, the reduction in number of medications from baseline at 12-month follow-up was significantly greater in the Hydrus Microstent versus the SLT group (a reduction of approximately 1.4 vs. 0.5 medications, to an average of approximately 0.9 versus 2.0 medications, respectively), but the absolute number of medications was not compared statistically.[62]

MIGS Versus Another MIGS

One Versus Two Versus iStent(s)

In a single RCT, the proportion of eyes requiring medications was numerically reduced from baseline in eyes that received one, two, or three iStent(s), but within- and between-group differences were not tested statistically.[59,60]

MIGS Versus Filtration Surgery

ECP Versus Glaucoma Drainage Device

In a retrospective cohort study, the mean number of medications was significantly reduced from baseline in both ECP and BGI groups at three to 24 months of follow-up (a reduction of approximately 1 to 1.5 medications from baseline), but was not significantly different between groups at any time point.[63]

In a non-randomized controlled clinical trial, the number of medications was numerically reduced from baseline in both ECP and AGI groups, but this was not tested statistically.[61] The mean number of medications was not significantly different between groups at baseline or at 24-month follow-up (approximately 2 versus 2.5 medications, respectively).[61]

Trabectome Versus Trabeculectomy With MMC

In a prospective cohort study, the number of medications was not reduced from baseline in the Trabectome group at any time point, but was significantly reduced from baseline in the Trabeculectomy group at one-day to six-month follow-up (approximately 2.34 versus 0.5 medications at six months for the Trabectome and Trabeculectomy groups, respectively; between-group comparisons were not tested statistically).[25]

In a retrospective cohort study, the number of medications was numerically reduced from baseline in both groups (not tested statistically) and the absolute number of medications was significantly greater in the Trabectome versus Trabeculectomy group at all follow-up time points (one to 30 months; at 30 months approximately 2.3 and 0.4 medications, respectively).[64]

Two iStent Injects Versus Trabeculectomy With MMC

In a prospective cohort study, the number of medications was significantly reduced from baseline in the two iStent Injects group at one-day and six-week follow-up, but not three- or six-month follow-up, and was significantly reduced from baseline in the Trabeculectomy group at all follow-up time points (at six months: 2.5 vs. 0.5 medications for the two iStent Injects and Trabeculectomy groups, respectively; between-group differences were not tested statistically).[25]

Trabectome or Two iStent Injects Versus Trabeculectomy With MMC

In a prospective cohort study, the number of medications was numerically reduced from baseline in the MIGS group (eyes that received either Trabectome or two iStent Injects grouped together; not tested statistically) and was significantly reduced from baseline in the Trabeculectomy group at one day to six months of follow-up.[25] The number of medications was significantly higher in the MIGS versus Trabeculectomy group at all follow-up time points.[25]

Xen45 With MMC Versus Trabeculectomy With MMC

In a retrospective cohort study, the median number of medications was numerically similar between Xen45 and Trabeculectomy groups at follow-up (not tested statistically; median follow-up duration of 15.0 and 17.8 months, respectively).[65]

Visual Field

A detailed summary of findings is provided in Table 35, Appendix 13.

MIGS Versus Pharmacotherapy

Two iStents Versus Travoprost

In a single RCT, VF (mean deviation and pattern standard deviation) was numerically similar between groups and across time points (baseline through 36-month follow-up) but this was not tested statistically.[58]

MIGS Versus Another MIGS

One Versus Two Versus Three iStent(s)

In a single RCT, the change in VF from screening to 42-month follow-up was not significantly different between the one, two, or three iStent(s) groups; whether the absolute VF was different from screening within groups at 18- or 42-month follow-up was not tested statistically.[59,60]

Visual Acuity

A detailed summary of findings is provided in Table 36, Appendix 13.

MIGS Versus Pharmacotherapy

Two iStents Versus Travoprost, or Two iStent Injects Versus Latanoprost + Timolol

In two RCTs, BCVA was measured but not compared at follow-up between either the two iStents and Travoprost[58] or the two iStent Injects and Latanoprost + Timolol groups.[36]

MIGS Versus Laser Therapy

Hydrus Microstent Versus SLT

In a single prospective cohort study, VA was not significantly different between Hydrus Microstent and SLT at baseline, and was not significantly different from baseline at 12-month follow-up in either group.[62] VA was not compared between groups at follow-up.[62]

MIGS Versus Another MIGS

One Versus Two Versus Three iStent(s)

In a single RCT, BCVA was numerically similar between the one, two, or three iStent groups at baseline or from one to 42 months of follow-up, but this was not tested statistically.[59,60]

MIGS Versus Filtration Surgery

ECP Versus Glaucoma Drainage Device

In a non-randomized controlled clinical trial, VA was not significantly different between the ECP and AGI groups at baseline or 12-month follow-up.[61]

Trabectome Versus Trabeculectomy With MMC

In a prospective cohort study, VA was numerically similar between the Trabectome and Trabeculectomy groups at baseline or six-month follow-up, but between-group differences were not tested statistically.[25] In a retrospective cohort study, VA was not different from baseline at the 12- or 24-month follow-up in either group, but was significantly better in the Trabectome versus Trabeculectomy group at all time points.[64]

Two iStent Injects Versus Trabeculectomy With MMC

In a prospective cohort study, VA was numerically similar between the two iStent Injects and Trabeculectomy groups at baseline or six-month follow-up, but between-group differences were not tested statistically.[25]

Trabectome or Two iStent Injects Versus Trabeculectomy With MMC

In a prospective cohort study, eyes that received Trabectome or two iStent Injects were grouped together as "MIGS."[25] VA was significantly better in MIGS versus Trabeculectomy at one-day post-operative, but was not significantly different between groups at any other time point up to six months of follow-up.[25]

Xen45 With MMC Versus Trabeculectomy With MMC

In a retrospective cohort study, median BCVA was not significantly different between Xen45 and Trabeculectomy groups at follow-up (with a median follow-up duration of 15.0 and 17.8 months, respectively).[65]

Research Question 2: What is the comparative safety of MIGS versus each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?

A detailed summary of findings is provided in Table 37, Appendix 13. A list of AEs and their categorization as "major" or "minor" is found in Table 27, Appendix 3.

MIGS Versus Pharmacotherapy

Two iStents Versus Travoprost, or Two iStent Injects Versus Latanoprost + Timolol

In two RCTs, AEs were considered minor in all treatment groups.[36,58] The incidence of AEs was < 2% each,[36,58] except for progression of cataract, which was 20% and 17% in the two iStents and Travoprost groups, respectively, in one study.[58]

MIGS Versus Laser Therapy

Hydrus Microstent Versus SLT

In a single prospective cohort study, AEs were transient (< 7 days) and minor in both Hydrus Microstent and SLT groups.[62] The incidence of AEs ranged from 6.5% (IOP spike in the Hydrus Microstent group) to 40% (eye discomfort in the SLT group; not reported in the Hydrus Microstent group).[62]

MIGS Versus Another MIGS

One Versus Two Versus Three iStent(s)

In a single RCT, there were no AEs in any of the one, two, or three iStent groups.[59,60] Secondary cataract surgery was required in up to 13% of eyes in each group by 42-month follow-up; the requirement was numerically similar between groups; however, this was not compared statistically.[59,60]

MIGS Versus Filtration Surgery

ECP Versus Glaucoma Drainage Device

In a retrospective cohort[63] and non-randomized controlled clinical trial,[61] there were no differences in AEs between ECP and GDD groups, except for shallow anterior chamber (a minor complication), which occurred in significantly fewer eyes in the ECP versus AGI group.[61] Major complications (failure of corneal graft, retinal detachment, tube exposure, endophalmitis, phthisis bulbi) occurred in both ECP and AGI groups in one study, with incidence ranging from 2.9% to 11.8%, but with no significant differences between groups.[61]

Trabectome Versus Trabeculectomy With MMC

In a retrospective cohort study, there were significantly more AEs in the Trabectome (100%) versus Trabeculectomy (approximately 38%) group when hyphema was included.[64] When hyphema was excluded, there were significantly fewer AEs in the Trabectome versus Trabeculectomy group (approximately 4% and 35%, respectively).[64] All AEs were minor, except for persistent hypotony and bullous keratopathy, which occurred in approximately 5% and 1%, respectively, in the Trabeculectomy group (0% in Trabectome group, but not compared statistically).[64] Secondary surgery was required significantly more often in the Trabectome versus Trabeculectomy group (approximately 44% and 11%, respectively).[64]

Xen45 With MMC Versus Trabeculectomy With MMC

In a retrospective cohort study, the incidence of AEs was numerically similar between Xen45 and Trabeculectomy groups; however, this was not tested statistically.[65] Major complications (hypotony maculopathy, corneal decompensation, and malignant glaucoma) occurred in both groups, with incidence ranging from 0% to 2.2% across groups.[65] Exposed Xen45, a major complication unique to the Xen45 group, occurred in one eye (0.5%). Numerically fewer post-operative interventions were required in the Xen45 (63.2%) versus the Trabeculectomy (97.6%) group, but this was not compared statistically. There was no difference between groups in the requirement for secondary glaucoma surgery (10.3% and 5.3% for Xen45 and Trabeculectomy groups, respectively).[65]

Research Question 3: What is the comparative clinical effectiveness of MIGS performed in combination with cataract surgery versus a) a different MIGS plus cataract surgery, b) filtration surgery plus cataract surgery, or c) cataract surgery alone for the treatment of glaucoma in adults?

Intraocular Pressure

A detailed summary of findings is provided in Table 38 and Table 39, Appendix 13. IOP was measured without medication washout unless otherwise stated.

MIGS + Cataract Surgery Versus Cataract Surgery Alone

ECP + Phaco Versus Phaco Alone

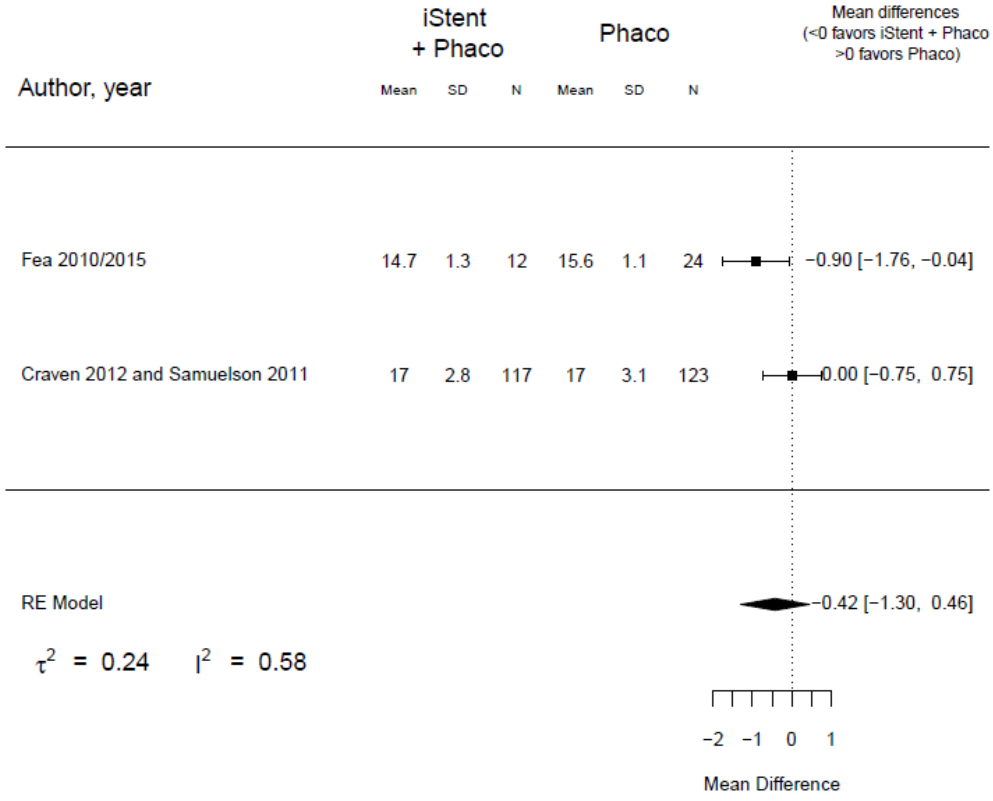
In three out of four retrospective cohort studies, IOP was reduced from baseline in both groups (to approximately 14 mm Hg to 17.5 mm Hg) but was not different between groups at up to 36 months of follow-up.[73-75] In the fourth retrospective cohort study, IOP was reduced from baseline at mean follow-up of 21 months in the ECP + Phaco group (to approximately 14 mm Hg) but was not reported in the Phaco alone group.[72]

In the prospective cohort study, IOP was significantly reduced from baseline from six to 36 months of follow-up but was significantly lower in the ECP + Phaco group versus the Phaco alone group (approximately 15 mm Hg versus 17 mm Hg, respectively, at 36 months).[84]

iStent + Phaco Versus Phaco Alone

In both RCTs, IOP was not significantly different between the iStent + Phaco and Phaco alone groups at baseline.[34,66-68] In one RCT, IOP was not significantly reduced from baseline in either the iStent + Phaco or Phaco alone group at 12 to 48 months of follow-up, and was significantly lower at both the medicated (15 month) and the unmedicated (16 month) follow-up in the iStent + Phaco versus Phaco alone groups, but was not different between groups at 48-month follow-up (approximately 16 mm Hg versus 17 mm Hg without medication washout, respectively).[66,67] In the second RCT, IOP was numerically similar between groups (approximately 17 mm Hg at 12- and 24-month follow-up) but statistical comparisons were not reported.[34,68] When data from the RCTs were pooled in meta-analysis, there was no significant difference between groups in IOP at 12-month follow-up (mean difference = –0.42 mm Hg; 95% CI, –1.30 to 0.46; $P = 0.34$; Figure 2).[34,66-68] Statistical heterogeneity was substantial ($I^2 = 58.47\%$).[34,66-68]

Figure 2: Mean Difference (95% Confidence Interval) in Intraocular Pressure Between The iStent + Phaco and Phaco Alone Groups at 12-Month Follow-Up



RE = random effects; SD = standard deviation.

Two iStents + Phaco Versus Phaco Alone

In an RCT, IOP was significantly lower in the two iStents + Phaco group versus Phaco alone at one to 12 months of follow-up (approximately a 2 mm Hg to 4 mm Hg difference between groups).[69] In one retrospective cohort study, there was inconsistent reporting (i.e., different values reported in abstract, tables, and text), so interpretation of findings was unclear.[76]

CyPass Micro-Stent + Phaco Versus Phaco Alone

In a single RCT, the reduction in IOP from baseline was significantly greater in the CyPass Micro-Stent + Phaco versus Phaco alone group at 12- and 24-month follow-up (between-group difference in washed-out IOP ~2 mm Hg).[70] Similarly, a significantly greater proportion of eyes achieved a ≥ 20% reduction in washed-out IOP from baseline at 12 and 24 months of follow-up in the CyPass Micro-Stent + Phaco versus Phaco alone group.[70] The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the MDALL and is therefore included in this report.

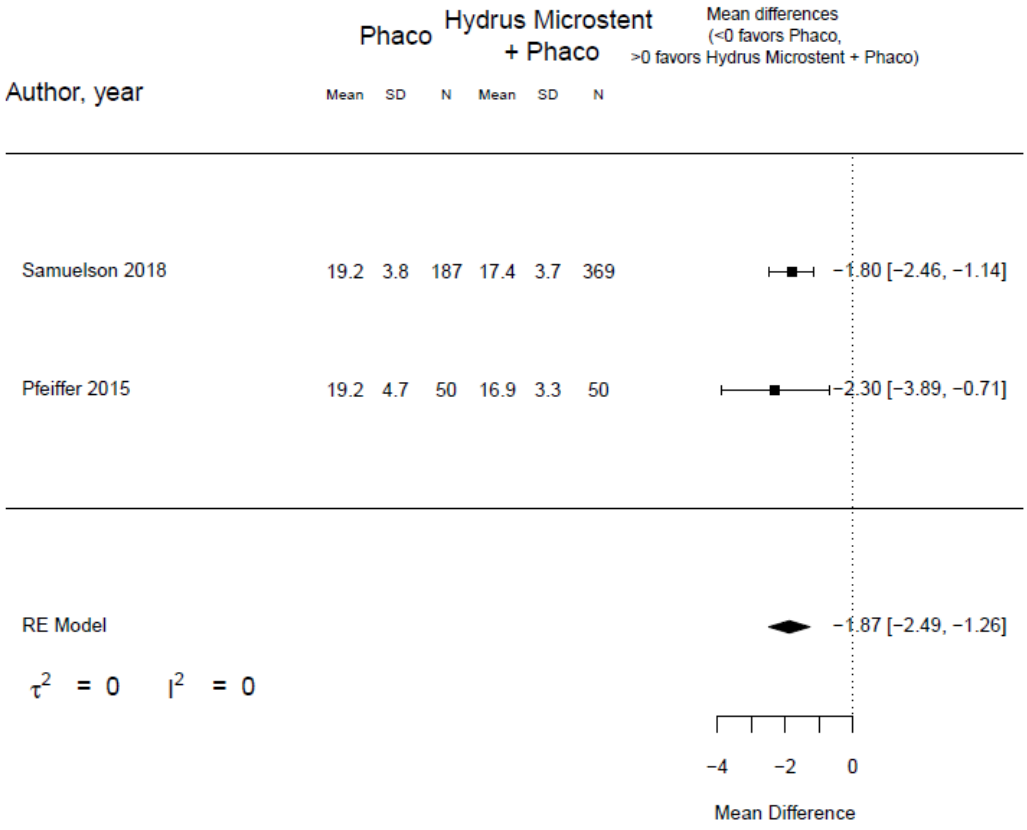
Hydrus Microstent + Phaco Versus Phaco Alone

In one RCT, washed-out diurnal IOP was reduced from baseline in both groups and was not different between groups at 12-month follow-up, but was significantly lower in the Hydrus Microstent + Phaco versus Phaco alone group at 24-month follow-up (washed-out diurnal IOP approximately 17 mm Hg versus 19 mm Hg, respectively).[71] Similarly, at 24 months (but not 12 months) a significantly greater proportion of eyes in the Hydrus Microstent + Phaco group achieved a ≥ 20% reduction in washed-out IOP from baseline.[71]

In the second RCT, the reduction in washed-out modified diurnal IOP from baseline was significantly greater in the Hydrus Microstent + Phaco versus Phaco alone group at 12- and 24-month follow-up (the washed-out modified diurnal IOP was approximately 17 mm Hg versus 19 mm Hg, respectively, at 24 months).[88] Similarly, a significantly greater proportion of eyes in the Hydrus Microstent + Phaco versus Phaco alone group had ≥ 20%, 30%, or 40% reductions in washed-out modified diurnal IOP at 24 months.[88]

When data from the RCTs were pooled in meta-analysis, the washed-out diurnal IOP was significantly lower in the Hydrus Microstent + Phaco versus Phaco alone group at 24-month follow-up (mean difference = –1.87 mm Hg; 95% CI, –2.49 to –1.26; $P < 0.0001$; Figure 3).[71,88] Statistical heterogeneity was low ($I^2 = 0.00\%$).[71,88]

Figure 3: Mean Difference (95% Confidence Interval) in Intraocular Pressure Between The Hydrus Microstent + Phaco and Phaco Alone Groups at 24-Month Follow-Up



RE = random effects; SD = standard deviation.

MIGS + Cataract Surgery Versus A Different MIGS + Cataract Surgery

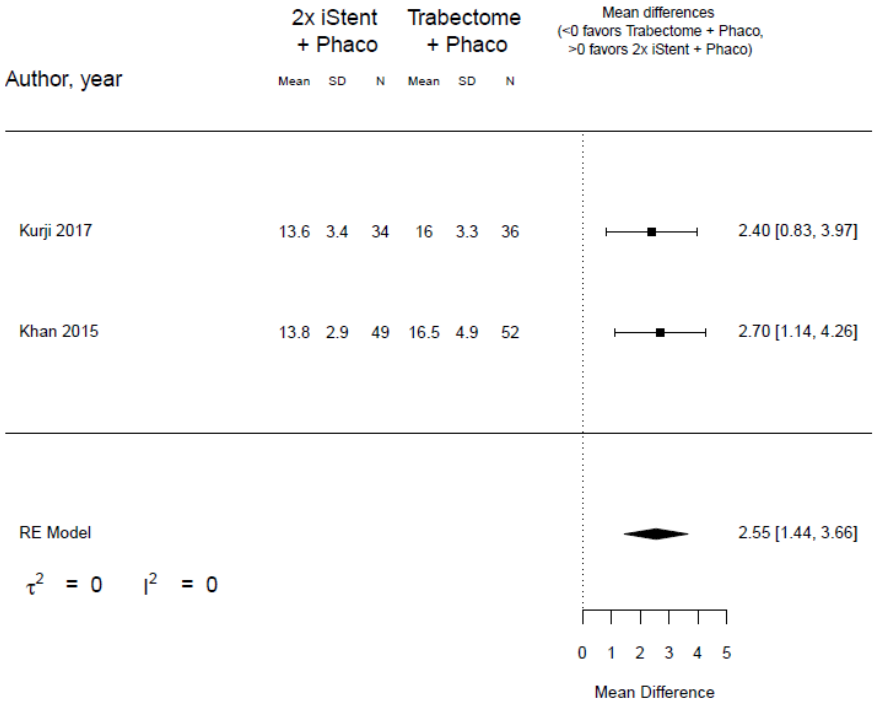
Goniotomy with KDB + Phaco Versus iStent + Phaco

In a retrospective cohort study, IOP was significantly reduced from baseline up to six-month follow-up in both groups, and the reduction was significantly greater in the KDB + Phaco versus iStent + Phaco group up to six-month follow-up (at six months, mean reduction was 4.2 mm Hg and 2.7 mm Hg, respectively).[86] A significantly greater proportion of eyes achieved an IOP reduction of ≥ 20% in the KDB + Phaco versus iStent + Phaco group at one week through six months of follow-up.[86]

Trabectome + Phaco Versus Two iStents + Phaco

In one retrospective cohort study, IOP was significantly higher in the Trabectome + Phaco versus two iStents + Phaco group at baseline, and was numerically higher at 12-month follow-up, but this did not reach statistical significance.[79] The reduction in IOP from baseline to follow-up was not significantly different between groups at 12 months.[79] In the second retrospective cohort study, IOP was not different between groups at baseline.[78] IOP was significantly reduced from baseline in both groups, but was significantly higher in the Trabectome + Phaco versus two iStents + Phaco groups at six- and 12-month follow-up (approximately 17 mm Hg versus 14 mm Hg, respectively).[78] When data from the studies were pooled in meta-analysis, IOP was significantly higher in Trabectome + Phaco versus two iStents + Phaco groups at the six-month follow-up (not taking into account differences at baseline; mean difference = 2.55 mm Hg; 95% CI, 1.44 to 3.66; $P < 0.0001$; Figure 4).[78,97] Statistical heterogeneity was low ($I^2 = 0.00\%$).[78,79]

Figure 4: Mean Difference [95% Confidence Interval] in Intraocular Pressure Between Trabectome + Phaco and Two iStents + Phaco Groups at Six-Month Follow-Up



2x = two devices; RE = random effects; SD = standard deviation.

Trabectome + MICS Versus Two iStent Injects + MICS

In a retrospective cohort study, IOP was significantly reduced from baseline in both groups but was not different between groups up to 12 months of follow-up (values shown only in a figure in the publication).[77]

Different Numbers of iStents + Phaco

In a retrospective cohort study, IOP was significantly reduced from baseline to 12-month follow-up (by approximately 2 mm Hg to 4 mm Hg), but was not different between groups with one or two iStent(s) + Phaco at any time point.[80]

In a non-randomized controlled clinical trial, IOP was significantly reduced from baseline up to 12-month follow-up (by approximately 4 mm Hg), but was not different between the two or three iStents + Phaco groups at any time point.[83] The proportion of eyes achieving an IOP of ≤15 mm Hg at 12-month follow-up was only reported in the two iStents + Phaco group (75%).[83]

ECP + iStent + Phaco Versus iStent + Phaco

In a retrospective cohort study, IOP reductions were significantly greater at 12-month follow-up in the ECP + iStent + Phaco versus iStent + Phaco group (with mean reductions of 7.14 mm Hg and 4.48 mm Hg to approximately 14 mm Hg versus 16 mm Hg, respectively).[81]

ECP + Phaco Versus Trabectome + Phaco

In a retrospective cohort study, IOP was numerically reduced from baseline in both ECP + Phaco and Trabectome + Phaco groups up to 12 months of follow-up (by ~3 mm Hg to 4 mm Hg) but this was not tested statistically.[89] IOP was not significantly different between groups from one-week to 12-month follow-up.[89]

MIGS + Cataract Surgery Versus Filtration Surgery + Cataract Surgery

Trabectome + Phaco Versus Trabeculectomy With MMC + Phaco

In a single RCT, IOP was numerically reduced from baseline at six and 12 months of follow-up in both groups (by approximately 3 mm Hg to 7 mm Hg), but this did not reach statistical significance; IOP was not significantly different between groups at baseline or any follow-up time point (at 12 months, approximately 17 mm Hg in both groups).[87]

Trabectome + Phaco Versus Trabeculotomy + Phaco

In a cohort study in which data were measured retrospectively (Trabeculotomy + Phaco) and prospectively (Trabectome + Phaco), IOP was numerically reduced from baseline from three to 36 months of follow-up in both groups (by approximately 6 mm Hg to 9 mm Hg), but this was not tested statistically; IOP was not significantly different between groups at baseline or any follow-up time point (approximately 14 mm Hg at 36 months in both groups).[85]

ECP + Phaco Versus Trabeculectomy With MMC + Phaco

In a retrospective cohort study, IOP was not significantly different between groups at baseline or six-month follow-up (at six months, approximately 13 mm Hg to 14 mm Hg in both groups).[82] IOP was transiently greater post-operative (one day) in the ECP + Phaco group versus the Trabeculectomy + Phaco group.[82]

Number of Glaucoma Medications

A detailed summary of findings is provided in Table 40, Appendix 13.

MIGS + Cataract Surgery Versus Cataract Surgery Alone

ECP + Phaco Versus Phaco Alone

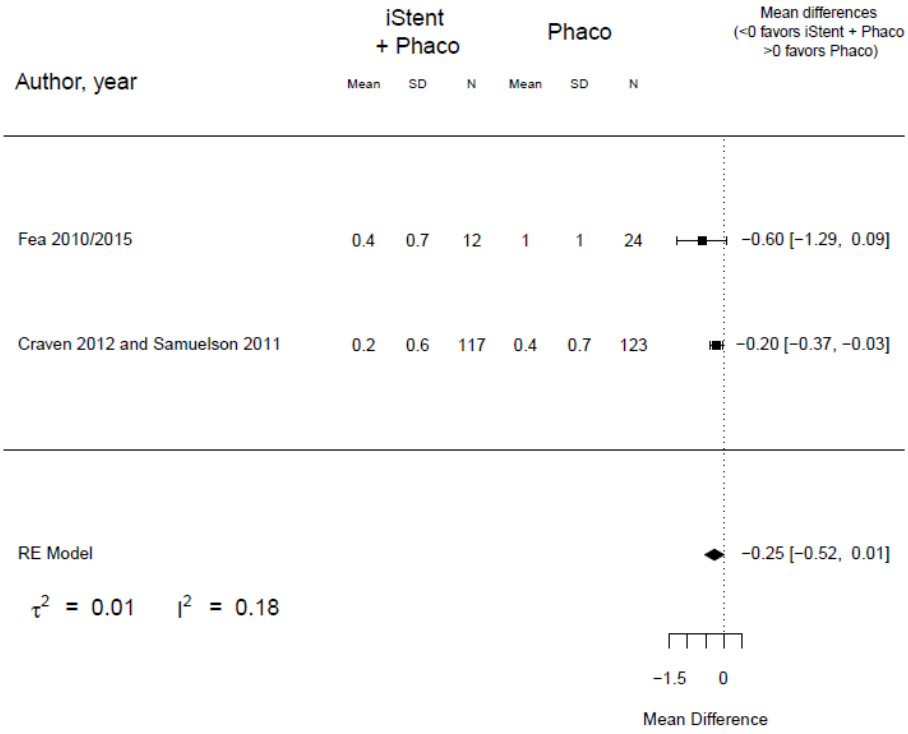
In three out of four retrospective cohort studies[73-75] the number of medications was significantly different between groups at baseline; in all cases, comparisons at follow-up tended to favour the group with the higher number of medications at baseline (i.e., groups with a higher number of medications at baseline also had a greater reduction; two-thirds of the studies[73,74] were in favour of ECP + Phaco and one-third in favour of Phaco alone[75]). In the fourth retrospective cohort study, the number of medications was reduced from baseline at mean follow-up of 21 months in the ECP + Phaco group, but was not reported in the Phaco alone group.[72]

In a prospective cohort study, the number of medications was significantly reduced from baseline to six to 36 months of follow-up in both groups (with the exception of 36 months in the Phaco alone group) but was significantly lower in ECP + Phaco versus Phaco alone at baseline and all follow-up time points.[84]

iStent + Phaco Versus Phaco Alone

In both RCTs, the number of medications was not significantly different between the iStent + Phaco and Phaco alone groups at baseline.[34,66-68] In one RCT, the number of medications was significantly reduced from baseline in both groups, and was numerically lower in the iStent + Phaco versus Phaco alone group at 12-month follow-up (but this was not tested statistically).[66,67] The number of medications was significantly lower in the iStent + Phaco versus Phaco alone group at 15-month follow-up (approximately 0.4 versus 1.3 medications, respectively) but not the 48-month follow-up (approximately 0.5 versus 0.9 medications, respectively).[66,67] In the second RCT, the number of medications was significantly lower in the iStent + Phaco group versus the Phaco alone group at the 12-month follow-up (approximately 0.2 versus 0.4 medications, respectively) but not the 24-month follow-up (approximately 0.3 versus 0.5 medications, respectively).[34,68] When data from the RCTs were pooled in meta-analysis, there was no significant difference between groups in the number of medications at 12-month follow-up (mean difference = –0.25 medications; 95% CI, –0.52 to 0.01; $P = 0.06$; Figure 5).[34,66,68,98] Statistical heterogeneity was low (I^2 = 17.86%).

Figure 5: Mean Difference [95% Confidence Interval] in Number of Glaucoma Medications Between iStent + Phaco and Phaco Alone Groups at 12-Month Follow-Up



RE = random effects; SD = standard deviation.

Two iStents + Phaco Versus Phaco Alone

In an RCT, the number of medications was not different between groups up to the two-month follow-up, but was significantly lower in the two iStents + Phaco versus Phaco alone group at 6- (approximately 0.1 versus 0.5 medications, respectively) and 12-month (approximately zero versus one medications, respectively) follow-up; the number of medications was numerically reduced from baseline in both groups, but statistical comparison with baseline was not conducted.[69]

In one retrospective cohort study, there was inconsistent reporting (i.e., different values reported in abstract, tables, and text) so interpretation of findings was unclear.[76]

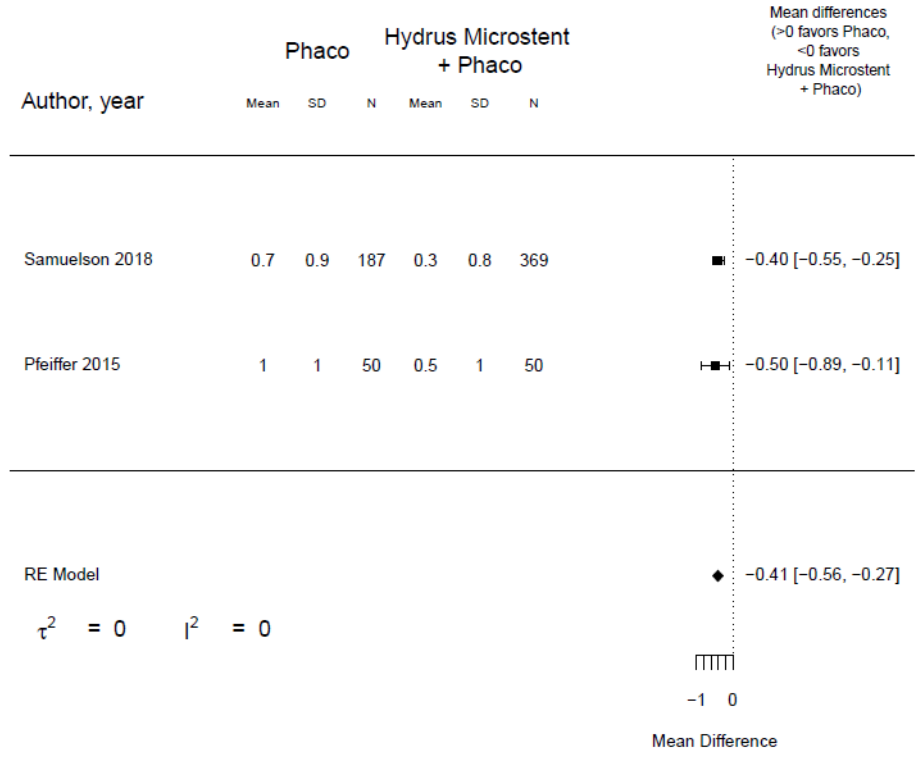
CyPass Micro-Stent + Phaco Versus Phaco Alone

In a single RCT, there were significantly fewer medications required in the CyPass Micro-Stent + Phaco versus Phaco alone group at 12- (approximately 0.2 versus 0.7 medications, respectively) and 24-month follow-up ("maintained" versus 0.6 medications, respectively); statistical comparison with baseline was not conducted.[70] The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the MDALL and is therefore included in this report.

Hydrus Microstent + Phaco Versus Phaco Alone

In one RCT, the number of medications was significantly reduced from baseline in both groups and was lower in the Hydrus Microstent + Phaco versus Phaco alone group at 24-month follow-up (approximately 0.5 versus 1.0 medications, respectively).[71] In the second RCT, the reduction in number of medications from baseline was significantly greater in the Hydrus Microstent + Phaco versus Phaco alone group at 12- and 24-month follow-up.[88] When data from the RCTs were pooled in meta-analysis, the number of medications was significantly lower in the Hydrus Microstent + Phaco versus Phaco alone group at 24-month follow-up (mean difference = –0.41 medications; 95% CI, –0.56 to –0.27; $P < 0.0001$; Figure 6).[71,88] Statistical heterogeneity was low ($I^2 = 0.00\%$).[71,88]

Figure 6: Mean Difference [95% Confidence Interval] in Number of Medications Between Hydrus Microstent + Phaco and Phaco Alone Groups at 24-Month Follow-Up



RE = random effects; SD = standard deviation.

MIGS + Cataract Surgery Versus A Different MIGS + Cataract Surgery

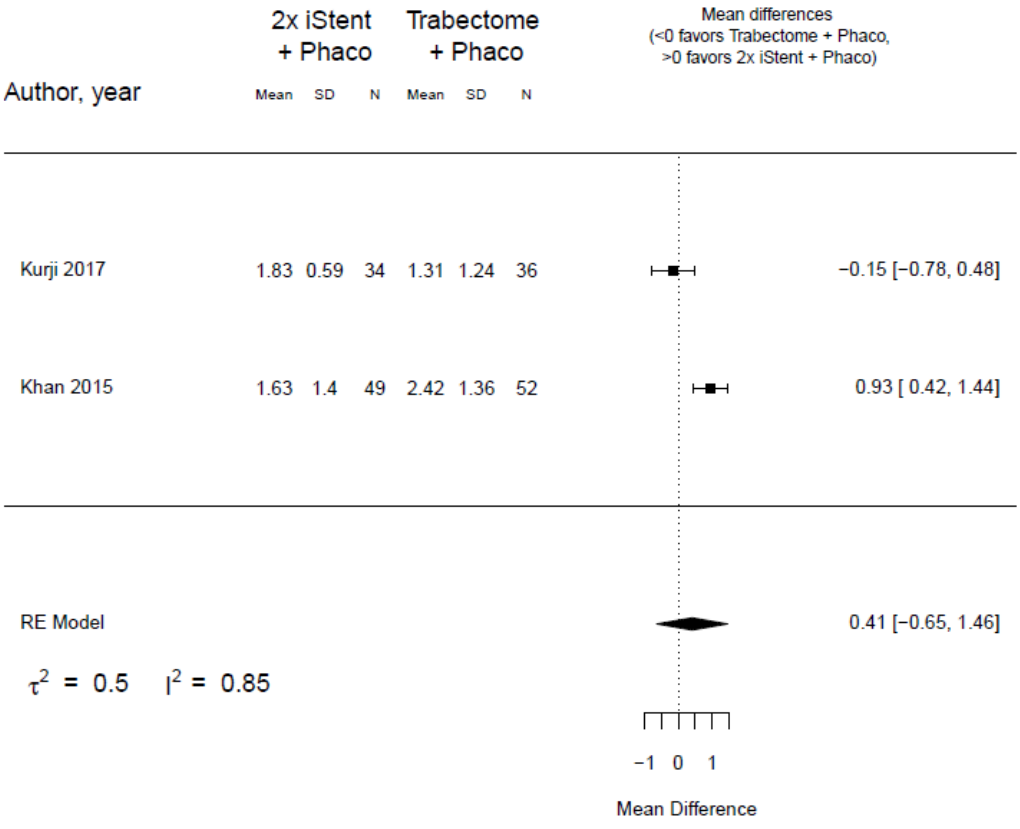
Goniotomy With KDB + Phaco Versus iStent + Phaco

In a retrospective cohort study, the number of medications was significantly lower, and the reduction in medications from baseline significantly greater, in the KDB + Phaco versus iStent + Phaco group at one-, three-, and six-month follow-up (at six months, approximately 0.6 versus 1.0 medications, respectively).[86]

Trabectome + Phaco Versus Two iStents + Phaco

In both retrospective cohort studies, the number of medications was not significantly different between the Trabectome + Phaco and iStent + Phaco groups at baseline.[78,79] In one retrospective cohort study, the absolute number of medications was not significantly different between groups at 6- or 12-month follow-up, but the reduction in number of medications from baseline was significantly greater in Trabectome + Phaco versus iStent + Phaco group at six-month (but not 12-month) follow-up.[79] In the second retrospective cohort study, the median number of medications was significantly reduced from baseline in both groups, but was significantly higher in the Trabectome + Phaco versus two iStents + Phaco group at three-, six-, and 12-month follow-up (approximately one versus two medications, respectively).[78] When data from the studies were pooled in meta-analysis, the number of medications was not significantly different between groups at 12-month follow-up (mean difference = 0.41 medications; 95% CI, –0.65 to 1.46; *P* = 0.4521; Figure 7).[78,79] Statistical heterogeneity was substantial (I^2 = 85.33%).[78,79]

Figure 7: Mean Difference (95% Confidence Interval) in Number of Glaucoma Medications Between Trabectome + Phaco and Two iStents + Phaco Alone Groups at 12-Month Follow-Up



2x = two devices; RE = random effects; SD = standard deviation.

Trabectome + MICS Versus Two iStent Injects + MICS

In a retrospective cohort study, the number of medications was significantly reduced from baseline in both groups but was not different between groups up to 12 months of follow-up (at 12 months, approximately 1.4 versus 1.3 medications for Trabectome + MICS and two iStent Injects + MICS, respectively).[77]

Different Numbers of iStents + Phaco

In a retrospective cohort study, at 12-month follow-up, the number of medications was significantly reduced from baseline only in the two iStents + Phaco group, and the number of medications was not significantly different between groups at any time point (at 12-month follow-up, approximately 1.7 versus 1.2 medications for one versus two iStent[s] groups, respectively).[80]

In a non-randomized controlled clinical trial, the number of medications was significantly reduced from baseline at 12-month follow-up in both groups, and was significantly higher in the two iStents + Phaco versus three iStents + Phaco group at six-month (approximately 1.2 versus 0.4 medications, respectively) and 12-month (approximately 1.0 versus 0.4 medications) follow-up.[83]

ECP + iStent + Phaco versus iStent + Phaco

In a retrospective cohort study, the number of medications was significantly greater at 12-month follow-up in ECP + iStent + Phaco versus iStent + Phaco (approximately 1.1 versus 0.62 medications, respectively).[81]

ECP + Phaco Versus Trabectome + Phaco

In retrospective cohort study, the number of medications was not significantly different between the ECP + Phaco and Trabectome + Phaco groups from one week to 12 months of follow-up.[89]

MIGS + Cataract Surgery Versus Filtration Surgery + Cataract Surgery

Trabectome + Phaco Versus Trabeculectomy With MMC + Phaco

In a single RCT, the number of medications was numerically reduced from baseline at six- and 12-month follow-up in both groups (by approximately one medication), but this did not reach statistical significance; the number of medications was not significantly different between groups at baseline or at any follow-up time point.[87]

Trabectome + Phaco Versus Trabeculotomy + Phaco

In a cohort study in which data were measured retrospectively (Trabeculotomy + Phaco) and prospectively (Trabectome + Phaco), the number of medications was significantly greater in the Trabectome + Phaco group versus the Trabeculotomy + Phaco group at three-, six-, and 12-month follow-up, but was not different between groups at 18, 24, or 26 months.[85]

ECP + Phaco Versus Trabeculectomy With MMC + Phaco

In a retrospective cohort study, the number of medications was not different between groups at baseline but was significantly higher in the ECP + Phaco group versus the Trabeculectomy + Phaco group at six-month follow-up (approximately 1.4 versus 0.5 medications, respectively).[82]

Visual Field

A detailed summary of findings is provided in Table 41, Appendix 13.

MIGS + Cataract Surgery Versus Cataract Surgery Alone

iStent + Phaco Versus Phaco Alone

In a single RCT, VF (mean deviation and pattern standard deviation) was not significantly different between the iStent + Phaco and Phaco alone groups at baseline or at 24-month follow-up; within-group comparisons from baseline to follow-up were not tested statistically.[34,68]

ECP + Phaco Versus Trabectome + Phaco

In a retrospective cohort study, the mean change in VF from baseline to 12 months of follow-up was not significantly different between the ECP + Phaco and Trabectome + Phaco groups.[89]

Visual Acuity

A detailed summary of findings is provided in Table 42, Appendix 13.

ECP + Phaco vs. Phaco Alone

In four retrospective cohort studies VA[72,73,75] and BCVA[74] were not different[74,75] between groups (or were numerically similar; no statistical comparisons[72,73]) at baseline or up to 36 months of follow-up.

iStent + Phaco Versus Phaco Alone

In a single RCT, CDVA was numerically similar between the iStent + Phaco and Phaco alone groups at baseline, 12-, and 24-month follow-up, but this was not tested statistically.[34,68] In one retrospective cohort study, there was inconsistent reporting (i.e., different values reported in abstract, tables, and text) and no numerical values reported at follow-up, so interpretation of findings was unclear.[76]

MIGS + Cataract Surgery Versus A Different MIGS + Cataract Surgery

Goniotomy with KDB + Phaco Versus iStent + Phaco

In a retrospective cohort study, BCVA improved significantly from baseline to six-month follow-up in both the KDB + Phaco and iStent + Phaco groups, and the change in BCVA was not significantly different between groups.[86]

Trabectome + Phaco Versus Two iStents + Phaco

In a retrospective cohort study, BCVA was not significantly different between the Trabectome + Phaco and two iStents + Phaco groups at baseline, and the change from baseline to 12-month follow-up was not significantly different between groups.[79]

Trabectome + MICS Versus Two iStent Injects + MICS

In a retrospective cohort study, BCVA was improved from baseline at 12-month follow-up in both the Trabectome + MICS and two iStent Injects + MICS groups, with no significant difference between groups at any time point.[77]

Different Numbers of iStents + Phaco

In a non-randomized controlled clinical trial, the proportion of eyes with a given CDVA was not different between the two and three iStents + Phaco groups at baseline and was numerically similar at 12-month follow-up, but this was not tested statistically.[83]

MIGS + Cataract Surgery Versus Filtration Surgery + Cataract Surgery

ECP + Phaco Versus Trabeculectomy With MMC + Phaco

In a retrospective cohort study, VA was significantly improved from baseline at six-month follow-up in both the ECP + Phaco and Trabeculectomy + Phaco groups and was not significantly different between groups.[82]

Research Question 4: What is the comparative safety of MIGS performed in combination with cataract surgery versus a) a different MIGS plus cataract surgery, b) filtration surgery plus cataract surgery, or c) cataract surgery alone for the treatment of glaucoma in adults?

A detailed summary of findings is provided in Table 43, Appendix 13. A list of AEs and their categorization as “major” or “minor” is found in Table 27, Appendix 3.

MIGS + Cataract Surgery Versus Cataract Surgery Alone

ECP + Phaco Versus Phaco Alone

AEs were compared statistically between groups in one out of three retrospective cohort studies, and the incidence of AEs was significantly greater in the ECP + Phaco group compared with Phaco alone.[73] In the other two retrospective cohort studies, the incidence of AEs was also numerically greater in the ECP + Phaco group, although this was not tested statistically.[72,75] In the prospective cohort study, the incidence of AEs was numerically similar between groups, but this was not tested statistically.[84] Across studies, AEs were minor in all treatment groups, except for the following major complications that occurred only in the ECP + Phaco groups (out of a total of 472 eyes): intracameral tissue plasminogen activator injection with synechiolysis (n = 1),[72] retinal detachment (n = 3),[73,75] and requirement for penetrating keratoplasty (n = 1).[75]

iStent + Phaco Versus Phaco Alone

In both RCTs, all AEs were considered minor and the incidence of AEs was numerically similar between the iStent + Phaco and Phaco alone groups, but this was not tested statistically.[34,66-68] Similarly, there the requirement for secondary glaucoma surgery in one RCT was numerically similar between groups (approximately 4.3% and 5.1% for iStent + Phaco and Phaco alone, respectively), but this was not tested statistically.[34,68]

Two iStents + Phaco Versus Phaco Alone

In a single RCT, the only reported AE was stent malposition; there were six malpositioned stents (18% of stents; number of eyes affected not reported) in the two iStents + Phaco group.[69]

CyPass Micro-Stent + Phaco Versus Phaco Alone

In a single RCT, there were no significant differences in AEs between groups, except for transient (≤ 30 day) BCVA loss, which occurred in significantly fewer eyes in the CyPass Micro-Stent + Phaco (8.8%) versus Phaco alone group (15.3%).[70] All AEs were considered minor, except for the following (no significant differences between groups): BCVA loss ≥ 10 letters (≥ 2 lines) at 24-month follow-up (1.1% in CyPass Micro-Stent + Phaco, 0% in Phaco alone); and VF loss progression (6.7% in CyPass Micro-Stent + Phaco, 9.9% in Phaco alone). There was no difference between groups in the requirement for secondary glaucoma surgery (5.5% and 5.3% for CyPass Micro-Stent + Phaco and Phaco alone, respectively).[70] In August 2018, the CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer due to five-year safety data from this same study.[37,38] As identified in a press release,[37] at five years the CyPass Micro-Stent + Phaco group had significantly greater endothelial cell loss compared with the group that had Phaco alone. Specifically, at five years there was an 20.4% reduction in endothelial cell density in the CyPass Micro-Stent + cataract surgery group compared with a 10.1% reduction in the control group (between-group difference, $P = 0.0032$). Similarly, "significant endothelial cell loss," defined as a reduction of greater than 30% was more common in the CyPass Micro-Stent group (27.2%) versus control (10%).[38]

Hydrus Microstent + Phaco Versus Phaco Alone

In one RCT, there were no significant differences in AEs between groups, except for focal peripheral anterior synechiae (minor) at two-year follow-up, which occurred in significantly more eyes in the Hydrus Microstent + Phaco (12.0%) versus Phaco alone (2.0%) group.[71] All AEs were considered minor, except for the following (no significant differences between groups; values for Hydrus Microstent + Phaco and Phaco alone, respectively): retinal detachment (0.0%, 2.0%); anterior ischemic optic neuropathy (0.0%, 2.0%); and BCVA loss >2 lines in year one (0.0%, 6.0%) or in year two (0.0%, 2.0%) of follow-up. In year one, there was no requirement for secondary glaucoma surgery in either group, and in year two there was no significant difference between groups in the requirement for secondary glaucoma surgery (2.1% and 4.1% for Hydrus Microstent + Phaco and Phaco alone, respectively).[71]

In a second RCT, the proportion of eyes with AEs was not compared statistically between groups.[88] All AEs were minor, except for the following (values for Hydrus Microstent + Phaco and Phaco alone, respectively): BCVA loss ≥ 2 lines for ≥ 3 months (1.4%, 1.6%), worsening of VF mean deviation by 2.5 decibels (dB) (4.3%, 5.3%), and development of neovascular glaucoma and secondary angle closure (1.0%, 0.5%).[88] The requirement for secondary glaucoma surgery not compared statistically between the Hydrus Microstent + Phaco (2.7%) and Phaco alone (1.1%) groups.[88]

MIGS + Cataract Surgery Versus A Different MIGS + Cataract Surgery

Goniotomy with KDB + Phaco Versus iStent + Phaco

In a retrospective cohort study, there were no significant differences between groups in AEs, except for IOP spikes, which occurred in significantly fewer eyes in the KDB + Phaco (6.5%) versus iStent + Phaco (12.6%) group.[86] All AEs were considered minor.[86]

Trabectome + Phaco Versus Two iStents + Phaco

In two retrospective cohort studies, all AEs were considered minor in both Trabectome + Phaco and Two iStents + Phaco groups.[78,79] In one study, there was a significantly greater

incidence of hyphema in the Trabectome + Phaco group, but no differences between groups in the incidence of any other AEs.[78] In the second study, there were significantly more AEs in the Trabectome + Phaco versus two iStents + Phaco group.[79] The requirement for secondary glaucoma surgery was not different between groups in one study[78] and was numerically greater in the Trabectome + Phaco group in the other,[79] but this was not tested statistically.

Trabectome + MICS Versus Two iStent Injects + MICS

In a retrospective cohort study, all AEs were considered minor and the incidence of AEs was numerically similar between the Trabectome + MICS and two iStent Injects + MICS groups, but this was not tested statistically.[77]

Different Numbers of iStents + Phaco

In a retrospective cohort study, there were no AEs in the two iStents + Phaco group, and a total of seven AEs in the one iStent + Phaco group.[80] All AEs were minor, except for one major complication in the iStent + Phaco group (central retinal vein occlusion leading to development of anterior-chamber neovascularization and neovascular glaucoma).[80]

In a non-randomized controlled clinical trial, AEs were not reported separately for each group.[83] All AEs were considered minor, except for death due to an unrelated systemic illness in one patient.[83]

ECP + iStent + Phaco Versus iStent + Phaco

In a retrospective cohort study, all AEs were considered minor.[81] The incidence of AEs and the requirement for secondary glaucoma surgery were numerically similar between the ECP + iStent + Phaco and iStent + Phaco groups, but this was not tested statistically.[81]

ECP + Phaco Versus Trabectome + Phaco

In a retrospective cohort study, the incidence of AEs was not compared statistically between the ECP + Phaco and Trabectome + Phaco groups, but all AEs were considered minor.[89] No eyes required secondary glaucoma surgery in either group.[89]

MIGS + Cataract Surgery Versus Filtration Surgery + Cataract Surgery

Trabectome + Phaco Versus Trabeculectomy With MMC + Phaco

In a single RCT, there was no significant difference in AEs between the Trabectome + Phaco and Trabeculectomy + Phaco groups overall.[87] All AEs were minor, except for hypotony maculopathy, which occurred in two eyes (22%) in the Trabeculectomy + Phaco group.[87] There was no significant difference between groups in the requirement for secondary glaucoma surgery (10% and 0% for Trabectome + Phaco and Trabeculectomy + Phaco, respectively).[87]

ECP + Phaco Versus Trabeculectomy With MMC + Phaco

In a retrospective cohort study, all AEs were considered minor.[82] IOP spikes occurred in significantly more eyes in the ECP + Phaco (50.0%) versus Trabeculectomy + Phaco (20.7%) groups, but between-group differences in other intraoperative or post-operative complications were not tested statistically.[82]

3.3 Integration of Outcomes

In this review, both IOP and number of glaucoma medications were secondary outcomes of interest. These outcomes are inherently related, in that the purpose of glaucoma medications is to reduce IOP. Therefore, it is necessary to jointly interpret intervention effects on IOP and number of glaucoma medications.

All studies included a measure of IOP as an outcome, and the number of glaucoma medications was an outcome in all studies except for the two in which pharmacotherapy was the comparator (Table 6).[36,58]

Overall, the impact on IOP was uncertain between MIGS and pharmacotherapy because there were no statistical comparisons.[36,58] The impact on IOP was not significantly different between MIGS and laser therapy (Hydrus Microstent versus SLT); however, the number of medications required to achieve the IOP was not compared statistically between groups.[62] MIGS versus each other were only compared in a single RCT; the reduction in IOP was incrementally greater with increasing numbers of iStents (i.e., one to three iStents), but the number of medications required to achieve the IOP was not compared statistically between groups.[59,60] In comparison to filtration surgery, the impact on IOP with MIGS was: 1) not significantly different (for ECP versus GDD,[61,63] Trabectome or two iStent Injects [grouped together] versus Trabeculectomy with MMC,[25] or Xen45 with MMC versus Trabeculectomy with MMC;[65] a greater number of medications was required in the MIGS groups in the latter two comparisons[25,65]), 2) unfavourable or not compared statistically (for Trabectome versus Trabeculectomy with MMC, and a greater number of medications was required in the Trabectome group),[25,64] or 3) not compared statistically or non-interpretable (for two iStent Injects versus Trabeculectomy with MMC, with a tendency for a greater number of medications required in the two iStent Injects group).[25]

In comparison to cataract surgery alone (Phaco), MIGS in combination with cataract surgery was as effective (i.e., no significant between-group difference for ECP + Phaco[73-75], iStent + Phaco[34,66-68]), more effective (ECP + Phaco,[84] two iStents + Phaco[69], CyPass Micro-Stent + Phaco,[70] or Hydrus Microstent + Phaco[71,88]), or non-evaluable (for ECP + Phaco in one study,[72] and one or two iStents + Phaco in one study)[76] with respect to IOP. Similarly, the number of glaucoma medications required was not different (for iStent + Phaco[34,66-68]) or was significantly lower (for two iStents + Phaco,[69] CyPass Micro-Stent + Phaco,[70] or Hydrus Microstent + Phaco[71,88]) with MIGS in combination with cataract surgery compared with cataract surgery (Phaco) alone (comparisons were non-evaluable for ECP + Phaco[73-75,84]).

In comparison with the effect of filtration surgery in combination with cataract surgery on IOP, the effect of MIGS in combination with cataract surgery was not significantly different (for Trabectome + Phaco versus Trabeculectomy with MMC + Phaco,[87] Trabectome + Phaco versus Trabeculotomy + Phaco,[85] or ECP + Phaco versus Trabeculectomy with MMC + Phaco[82]). Similarly, the number of glaucoma medications required was not significantly different,[85,87] except in one study in which a significantly greater number of medications was required in the ECP + Phaco group versus the Trabeculectomy with MMC + Phaco group.[82]

Different MIGS in combination with cataract surgery were compared with one another in eight studies.[77-81,83,86,89] Goniotomy with KDB was more favourable than iStent + Phaco with respect to IOP and number of medications in one study.[86] In a meta-analysis of two studies,[78,79] IOP was significantly lower following Trabectome + Phaco compared with two iStents + Phaco; however, IOP was also lower in Trabectome + Phaco at baseline in one of

the pooled studies,[79] making interpretation of findings unclear. There were no significant differences between Trabectome + Phaco and two iStents + Phaco with respect to number of medications.[78,79] When combined with a different type of cataract surgery (MICS), there was no significant difference in IOP or number of medications between Trabectome + MICS or two iStent Injects + MICS.[77] When combined with cataract surgery, the reduction in IOP was not significantly different in eyes treated with one to three iStents,[80,83] and the number of medications required was not different between one or two iStents,[80] but was significantly lower with three iStents.[83] In one study, IOP reductions were significantly greater in ECP + iStent + Phaco compared with iStent + Phaco, but the number of medications required was also significantly greater.[81] In the final study, neither IOP nor number of medications was significantly different between the ECP + Phaco and Trabectome + Phaco groups from one week to 12 months of follow-up.[89]

In most studies, the overall magnitude of change in IOP from baseline ranged from a reduction of approximately 1 mm Hg to 16 mm Hg at follow-up (which ranged from approximately 2 months[74] to four years[66]); this is a similar order of magnitude as normal diurnal fluctuations.[99] The largest reduction from baseline to follow-up was observed in a study in which patients had uncontrolled IOP at baseline (with mean approximately 41 mm Hg at baseline and a mean reduction of 19 mm Hg to 36 mm Hg).[61] Diurnal variation was only accounted for in the measurement of IOP in five[36,61,70,71,88] out of 32 studies. In addition, in most studies, IOP was measured without medication washout (with five exceptions,[59,60,66,67,70,71,88] not including studies in which pharmacotherapy was the comparator[36,58]), and in many cases either the number of medications was significantly different between groups[25,34,63,64,68,69,74-78,81-86] or was not evaluable (i.e., not reported in the comparator group[72] or not compared statistically between groups[73]). The method of measuring the number of glaucoma medications was not reported in any study.

3.4 Summary of Results

A detailed summary of study findings is provided in Appendix 13. In total, nine studies in 10 publications were identified that provided evidence on the clinical effectiveness or safety of MIGS versus comparators (research questions 1 and 2),[25,36,58-65] and 23 studies in 25 publications were identified that provided evidence on the clinical effectiveness or safety of MIGS in combination with cataract surgery versus comparators (research questions 3 and 4).[34,66-89] Mean patient age ranged from approximately 54[61] to 79[83] years across studies, men and women were equally represented, and the majority of patients were white. Across studies, the length of follow-up was at least 12 months in all but six studies[25,72,74,76,82,86] in which patients were followed for six months,[25,76,82,86] or in which the mean follow-up was 2.1 months in one group and 7.4 months in the other,[74] or the mean follow-up duration was 21 months (but was as little as two weeks).[72] All studies included primarily patients with OAG, and 19 studies also included patients with different types of glaucoma (e.g., angle-closure or pseudoexfoliation glaucoma; Appendix 10 includes further details). Information on glaucoma severity was reported in approximately two-thirds of included studies, and eyes with mild-to-moderate glaucoma were most commonly included, although ten studies also included eyes with advanced or severe glaucoma.[65,69,73,78-81,83,87,89]

The quality of the evidence ranged from “very low” to “high” across outcomes, comparisons and study designs (Appendix 13). The most common limitations of the evidence were: 1) serious risk of bias that reduced the level of confidence in the observed effects, and 2) serious imprecision (e.g., only a single study for a given comparison, no measures of variability, or wide variability leading to uncertainty about the true magnitude of the effect).

Overall, primarily in patients with mild-to-moderate OAG, there was insufficient evidence for the comparative effectiveness and safety of MIGS versus pharmacotherapy, laser therapy, different MIGS (i.e., one type of MIGS versus another), or filtration surgery. The clinical effectiveness of MIGS in combination with cataract surgery tended to be more favourable than cataract surgery alone; however, findings for comparative safety were mixed. There was insufficient evidence for the comparative clinical effectiveness and safety of MIGS in combination with cataract surgery versus filtration surgery in combination with cataract surgery. Most reported AEs were considered minor; however, the evidence for AEs was "very low" quality, and between-group differences were uncertain when major AEs were observed. There was no definitive evidence as to which MIGS might be preferable, either overall or for a subset of patients.

Clinical Effectiveness of MIGS (With Or Without Cataract Surgery) Versus Comparators

Overall, the evidence from nine primary studies regarding the comparative clinical effectiveness of MIGS was rated as "very low" to "low" in quality, and the evidence from 23 primary studies regarding the comparative clinical effectiveness of MIGS in combination with cataract surgery was rated as "very low" to "high" in quality (additional details are provided in the Quality Assessment: Overall Body of Evidence section, and Table 32to Table 36 and Table 38 to Table 43, Appendix 13).

In general, primarily in patients with mild-to-moderate OAG, there was insufficient evidence for the comparative clinical effectiveness and safety of MIGS versus pharmacotherapy, laser therapy, different MIGS, or filtration surgery. Different MIGS were compared with one another in nine studies[59,60,77-81,83,86,89] for six different comparisons, but there was insufficient evidence to establish whether any particular MIGS might have comparatively greater clinical effectiveness.

The primary outcome of interest, QoL, was measured in a single prospective cohort study that compared MIGS (Trabectome or two iStent Injects, separate or grouped together) with filtration surgery (Trabeculectomy with MMC).[25] In brief, differences in QoL between groups were not examined at baseline.[25] One out of 12 QoL parameters (colour vision) was significantly greater in the Trabectome versus Trabeculectomy group at six-month follow-up; however, whether the difference (approximately 13 points on a 100-point scale) was clinically meaningful is unclear; all other parameters were not significantly different between groups.[25] None of the 12 QoL parameters were significantly different between the two iStent Injects and Trabeculectomy groups, or between the MIGS (Trabectome or two iStent Injects combined) and Trabeculectomy groups, at six-month follow-up.[25]

With respect to IOP, the overall impact on IOP was uncertain for comparisons of MIGS and pharmacotherapy (very low-quality evidence from two studies) or different MIGS (very low-quality evidence from one study). The impact on IOP tended to be similar between MIGS laser therapy (very low-quality evidence from one study), and findings were mixed for comparisons of MIGS and filtration surgery (very low-quality evidence from five studies). In addition, in some (but not all) comparisons with filtration surgery, a greater number of medications were required in the MIGS groups. In comparison with cataract surgery alone, MIGS in combination with cataract surgery was as effective or more effective with respect to IOP (very low to high-quality evidence from 12 studies), and the number of medications required to achieve the IOP was not different or was significantly lower in the combined MIGS plus cataract surgery groups (very low to moderate quality evidence from 12 studies). In comparison with filtration surgery in combination with cataract surgery (very low-quality

evidence from three studies), MIGS + cataract surgery was as effective with respect to IOP, but in some cases a greater number of glaucoma medications was required to achieve this IOP. These findings are limited because, in the majority of studies, among other factors, diurnal variation in IOP was not accounted for in its measurement, IOP was measured without medication washout, and the method of measuring the number of glaucoma medications was not reported.

VF was assessed in four studies.[34,58-60,68,89] The impact on VF was unclear for the comparison of MIGS and pharmacotherapy (very low-quality evidence from one study and no statistical comparisons),[58] was not different significantly between different numbers of iStents (very low-quality evidence from one study),[59,60] was not significantly different between MIGS in combination with cataract surgery and cataract surgery alone (very low-quality evidence from one study),[34,68] and was not significantly different between different MIGS (ECP and Trabectome) in combination with cataract surgery (very low-quality evidence from one study).[89]

VA was measured but between-group differences were not tested statistically for comparisons of MIGS versus pharmacotherapy[36,58] or laser therapy,[62] or between different numbers of iStents[59,60] (all very low-quality evidence). In comparison to filtration surgery, the impact on VA with MIGS was not significantly different[25,61,63,65] or was not tested statistically[25,64] (very low-quality evidence from five studies). For comparisons of MIGS in combination with cataract surgery versus cataract surgery alone, between-group differences in VA were not statistically significant[72-75] or were unclear because there were no statistical comparisons (very low-quality evidence from six studies).[34,68] Similarly, VA was not significantly different between MIGS in combination with cataract surgery and filtration surgery in combination with cataract surgery (one study with very low-quality evidence).[82] VA was not significantly different in any comparisons of different MIGS in combination with cataract surgery (very low-quality evidence from four studies).[79,86,83] Notably, where reported, VA was measured by decimal chart, Snellen VA, or eye chart[58,72,75,79,83] or Snellen converted to logMAR.[65,73,74,82,86] These measures are not considered reliable, valid, or discriminative,[96] and therefore VA results should be interpreted with caution.

Safety of MIGS (With or Without Cataract Surgery) Versus Comparators

The evidence from eight primary studies regarding the comparative safety of MIGS, and 20 primary studies regarding the comparative safety of MIGS in combination with cataract surgery, was rated as “very low” quality (see Quality Assessment: Overall Body of Evidence and Table 37 and Table 43, Appendix 13, for further detail). The evidence was limited because the method of measuring AEs was not reported in any study, and whether there was any restriction on what was considered an AE or complication was not reported. Therefore, if no detail on a particular AE was reported in a given study, it was unclear whether this was because the particular AE did not occur or whether information on that AE was not collected. It was not possible to assess whether data on all patient-important AEs or harms were collected. In many cases, information on AEs was reported without statistical comparisons between groups.[34,36,58-60,62,65-69,72,75,77,80-84,88,89]

Recognizing these limitations, overall, primarily in patients with mild-to-moderate OAG, the comparative incidence of AEs was unclear for comparisons of MIGS versus pharmacotherapy,[36,58] laser therapy,[62] or other MIGS,[59,60] as there was insufficient evidence with statistical analyses (very low-quality evidence from four studies). For MIGS versus filtration surgery, there was very low-quality evidence from four studies and findings were

mixed (not statistically different,[61,63] favourable,[61,64] or unfavourable[64] for MIGS, or not tested statistically[65]).

There were mixed findings regarding the comparative safety of MIGS in combination with cataract surgery versus cataract surgery alone; in comparison to cataract surgery alone, the incidence of AEs with MIGS in combination with cataract surgery was: 1) not compared statistically,[34,66-69,72,75,84] 2) greater,[73] 3) not significantly different or lower,[70] or 4) not significantly different or higher.[71] The incidence of AEs with MIGS in combination with cataract surgery tended to be similar to the incidence with filtration surgery in combination with cataract surgery (very low-quality evidence from two studies), with the exception of IOP spikes, which occurred in significantly more eyes in the MIGS group in one study.

AEs were largely considered minor in all treatment groups. Major treatment-related complications were reported in only eleven studies, and differences between MIGS and comparators were either not tested statistically[64,65,70,72,73,75,80,87,88] (and were therefore uncertain) or were not significantly different.[61,71]

Where examined,[59,60,64,65,88,89] the requirement for secondary surgery was: similar between eyes with one, two, or three iStents (not tested statistically),[59,60] and was not different[65] or greater[64] in eyes with MIGS versus filtration surgery. The requirement for secondary surgery was not different (or numerically similar but not tested statistically[88]) between MIGS in combination with cataract surgery and cataract surgery alone[34,68,70,71] or filtration surgery plus cataract surgery.[87] The requirement for secondary surgery was either not significantly different[78,89] or not tested statistically[77,79,81] for comparisons of different MIGS in combination with cataract surgery.

4. Economic Evaluation

4.1 Methods

4.1.1 Literature Review

A review of the literature was conducted to identify published economic evaluations and costing studies in patients with glaucoma that may be applicable to the Canadian setting. No identified studies were conducted in a Canadian setting. Most of the studies focused on non-MIGS comparisons, such as pharmacotherapy, laser therapy, and surgical therapies.[100-103] While studies were identified that considered separately either the outcomes of costs or QoL associated with MIGS, these did not incorporate the effects of treatment with costs together and, as such, were not fully realized economic evaluations.[25,104]

Identified studies did not answer the research question posed in this HTA as no published Economic Evaluation has been undertaken to compare MIGS with various glaucoma treatments. In some instances, these studies did provide insight by informing the selection of input parameter values for this Economic Evaluation. The studies that informed this Economic Evaluation are described in more detail in later sections of the report.

Methods Overview

The objective of this study was to determine the cost-effectiveness of various types of MIGS procedures, with or without cataract surgery, compared with each other, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults.

This analysis was conducted according to a protocol developed a priori,[40] and incorporated the findings of a systematic clinical review on the relative efficacy and safety of MIGS, with or without cataract surgery, compared with the above listed comparators. The scope and analytical approach taken in this Economic Evaluation was therefore based on the availability of data identified from the Clinical Review.

Type of Economic Evaluation

According to the CADTH guidelines, the reference case of an Economic Evaluation should be cost-utility analysis with outcomes expressed as quality-adjusted life-years (QALYs).[105] Although the clinical condition and its potential treatments have no mortality effects, cost-utility analysis was considered the most appropriate given the different morbidity impacts related to the progression of glaucoma on vision. The main outcome of the Economic Evaluation was incremental cost per QALY gained, reported as the incremental cost-utility ratio (ICUR).

Interventions

As described in the previous section, it was concluded in the Clinical Review that it was not possible to determine relative effectiveness and safety among MIGS devices given the limited comparisons between alternative MIGS devices. Furthermore, the Clinical Review reported 24 unique pairwise comparisons and, given the heterogeneity between studies, indirect treatment comparison to evaluate the potential treatment effects of multiple interventions was deemed inappropriate. As such, the Economic Evaluation focused on comparing MIGS, as a group of interventions, with other glaucoma treatments to assess the potential cost-effectiveness range associated with MIGS. Furthermore, in alignment with the Clinical Review, only pairwise comparisons were considered as part of the Economic Evaluation. In particular, five broad comparisons by class of treatment were evaluated based on the availability of the clinical data:

Without cataract surgery (models 1 to 3):

1. MIGS versus pharmacotherapy
2. MIGS versus laser therapy
3. MIGS versus filtration surgery (i.e., GDDs or Trabeculectomy).

With cataract surgery (models 4 to 5):

4. MIGS + cataract surgery versus cataract surgery
5. MIGS + cataract surgery versus filtration surgery + cataract surgery.

Target Populations

The target population modelled was adults with acquired glaucoma, with an average age ranging from 64 to 72 years old, and reflected the characteristics of patients enrolled in the studies that were identified from the Clinical Review (Table 8).

As the potential use of MIGS within the treatment pathway for glaucoma is unclear, it is important to define disease severity at baseline to allow modelling patients' disease progression within each model. While the clinical expert consulted on this project indicated that the staging of glaucoma is evolving, the commonly used Hodapp-Parrish-Anderson grading scale was employed to define disease severity. In this scale, VF scores correspond

to the following severity: 1) mild: 0 to –6 dB; 2) moderate: –6.01 to –12 dB; 3) advanced: –12.01 to –20 dB; and 4) severe/blindness: < –20 dB.[106]

Baseline disease severity in each model was based on the baseline characteristics of patients recruited in the clinical studies. This approach was further validated and confirmed appropriate by the clinical expert. Patients in Models 2 (MIGS versus laser therapy; average baseline VF –5.74 dB)[62] and 4 (MIGS + cataract surgery versus cataract surgery alone; weighted average baseline VF –4.13 dB)[71,88] reflected those with mild-stage glaucoma and patients started in moderate-stage glaucoma in Model 1 (MIGS versus pharmacotherapy; average baseline VF –6.65 dB)[36]. For Model 3, as populations with both moderate- (Model 3a; average baseline VF –6.45 dB)[64] and advanced-stage (Model 3b; average baseline VF –16.64 dB)[63] glaucoma were identified in the clinical studies, both populations were examined separately. Finally, advanced-stage patients were considered in Model 5 (average baseline VF –13.49 dB),[85] again reflecting the characteristics of patients recruited in these studies.

Table 8: Baseline Patient Characteristics Associated With Each Model

Model	Baseline Age	Average Baseline VF	Glaucoma Stage[a]
Model 1: MIGS vs. pharmacotherapy	64	–6.65 dB	Moderate
Model 2: MIGS vs. laser therapy	70	–5.74 dB	Mild
Model 3a: MIGS vs. filtration surgery	65	–6.45 dB	Moderate
Model 3b: MIGS vs. filtration surgery	65	–16.64 dB	Advanced
Model 4: MIGS + cataract surgery vs. cataract surgery alone	72	–4.13 dB	Mild
Model 5: MIGS + cataract surgery vs. filtration surgery + cataract surgery	71	–13.49 dB	Advanced

dB = decibels; MIGS = minimally invasive glaucoma surgery; VF = visual field; vs. = versus.

[a] According to the Hodapp-Parish-Anderson grading scale.

4.1.2 Perspective

We conducted the analysis from the Canadian health care payer's perspective. Accordingly, direct and indirect medical costs were captured, including device or drug costs, physician fees, operating room (OR), ophthalmologist visits, and tests, as well as complications. Although the original project protocol had noted interest in considering a societal perspective,[40] this was omitted in the final report given that the average baseline age of patients in the economic analysis was between 64 to 72 years of age and most would be considered retired.

4.1.3 Time Horizon and Discounting

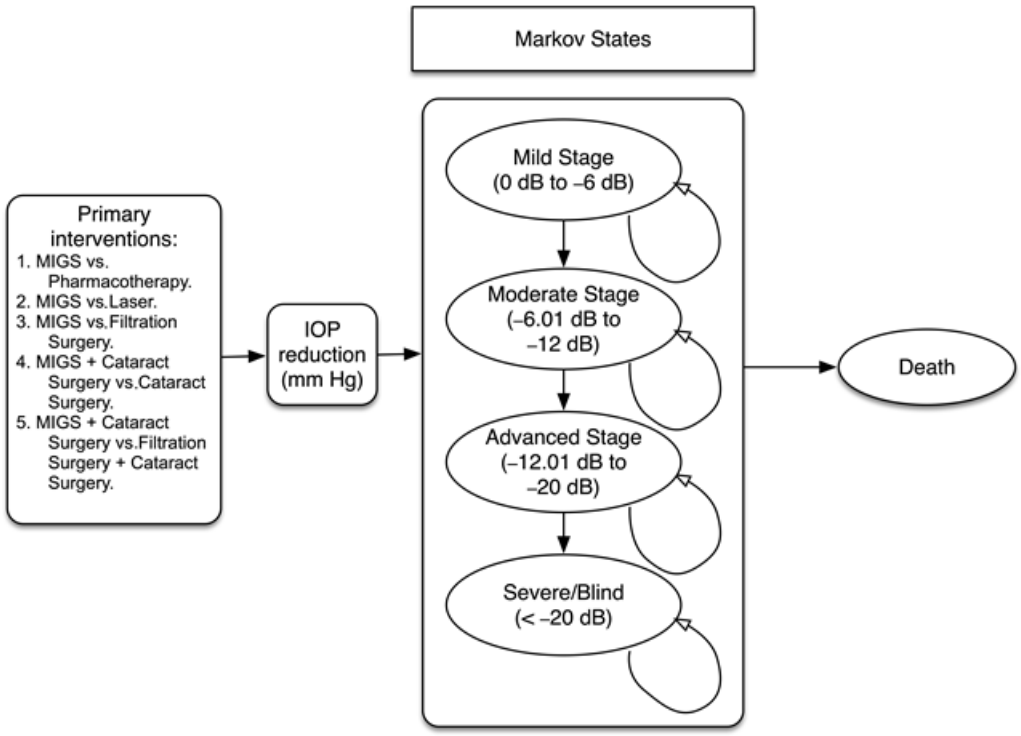
The time horizon for this analysis was lifetime (up to 95 years old), with a one-year time horizon assessed in sensitivity analysis (to validate against the majority of clinical studies that reported outcomes at one year). An annual discount rate of 1.5% was used per the CADTH guidelines for economic evaluations.[105] Rates of 0% and 5% were considered in sensitivity analyses.

4.1.4 Model Structure

A Markov model was developed to estimate the cost-effectiveness of MIGS versus other treatments in adult patients with glaucoma. The cycle length of the model was one month. As previously noted, the model categorized patients into disease severity based on the Hodapp-Parrish-Anderson score. This allowed consideration of patients entering the model at different severities of the disease. Furthermore, as the clinical management and treatment of glaucoma is dependent on the extent of glaucomatous damage, these categories allowed modelling of potential changes in the clinical care pathway of glaucoma over time with respect to vision-related QoL and associated resource use. Health states in the model were defined according to Hodapp-Parrish-Anderson staging[106] and were as follows: 1) Mild Stage: 0 to –6 dB; 2) Moderate Stage: –6.01 to –12 dB; 3) Advanced Stage: 12.01 to –20 dB and 4) Severe/Blindness < –20 dB, with an absorbing death state.

A graphical representation of model structure is shown in Figure 8. It was assumed that patients without treatment progressed annually at a rate of –0.6 dB, according to the Early Manifest Glaucoma Trial.[107] Once patients progressed to the next stage of severity, they could not reverse in disease severity to a more proximal glaucoma health state. When patients reached advanced-stage glaucoma (< –12dB), Trabeculectomy was performed. For patients who started in the advanced disease stage (models 3b and 5), it was assumed that filtration surgery was the last option, and as such no subsequent treatment was modelled. A summary of subsequent treatments for each model is summarized in Table 9.

Figure 8 : Outline of Model Structure and Health States



dB = decibels; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; vs. = versus.

Table 9: Subsequent Treatments

Category	Subsequent Treatment
Model 1: MIGS vs. pharmacotherapy	Trabeculectomy for both comparators when VF progresses to –12.01 dB.
Model 2: MIGS vs. laser therapy	Trabeculectomy for both comparators when VF progresses to –12.01 dB.
Model 3a: MIGS vs. filtration surgery (early stage)	Trabeculectomy for both comparators when VF progresses to –12.01 dB.
Model 3b: MIGS vs. filtration surgery (late stage)	NA (assumed last treatment option).
Model 4: MIGS + cataract surgery vs. cataract surgery alone	Trabeculectomy for both comparators when VF progresses to –12.01 dB.
Model 5: MIGS + cataract surgery vs. filtration surgery + cataract surgery (late stage)	NA (assumed last treatment option).

dB = decibels; MIGS = minimally invasive glaucoma surgery; NA = not applicable; VF = visual field; vs. = versus.

4.1.5 Data Inputs

Clinical Inputs and Natural History of Disease

As glaucoma and its treatment have long-term consequences, a lifetime model was considered appropriate.[105] However, the included clinical studies all reported on surrogate outcomes over a short time period (typically a one-year study duration). Modelling of disease progression and treatment was necessary to project long-term costs and consequences. A one-year model was also conducted in a non–reference-case analysis to explore this.

Mortality rates were obtained from the Canadian Life Tables 2014 to 2016[108] and were influenced by age; mortality was assumed to be the same for all VF stages (no increased risk of death with more severe VF deficit). When reported, the average baseline VF was informed by the clinical studies that were used to inform the model (Table 10). The starting age was calculated based on the weighted average from included clinical studies for each model category.

Relative treatment efficacy in the economic model was based on the most commonly reported outcomes from the identified studies of the Clinical Review: IOP reduction and medication reduction.

To estimate the rate of glaucoma progression defined by VF, from change in IOP, modelling was necessary. The following approach was taken to derive the relationship between rate of progression and change in IOP. In the Early Manifest Glaucoma Trial, the rate of progression of glaucoma in untreated patients was reported to be –0.05 dB per month (converted to –0.6 dB per year).[107] Treatment in this trial (i.e., laser therapy with medication) resulted in an IOP reduction of 5.1 mm Hg with a corresponding reduction in the rate of VF progression from –0.05 dB (baseline) to –0.03 dB per month; this change in IOP corresponded to a reduction factor of 0.6 dB for VF progression (i.e., –0.03 dB and –0.05 dB). The standardized reduction per unit of IOP reduction was then calculated as follows:

$$Factor^{(1/IOP\ reduction)}$$
$$= 0.6^{(1/5.1)}$$
$$= 0.905$$

Using this association, the change in disease progression from treatment was estimated using the IOP reduction that was reported from the clinical studies. For example, in a study comparing two iStent Injects (2nd generation) versus pharmacotherapy (i.e., Latanoprost + Timolol),[36] the annual IOP reduction was 12.2 mm Hg and 11.6 mm Hg, respectively. As such, the annual rate of disease progression with treatment was calculated using the following equation:

$$annual\ baseline\ progression\ in\ untreated\ patients * standardized\ reduction^{(annual\ IOP\ reduction)}$$
Two iStent Injects: $= -0.6 * 0.905^{12.2} = -0.177$ dB
Pharmacotherapy: $= -0.6 * 0.905^{11.6} = -0.188$ dB

Of note, other observational studies have reported on the association between change in IOP and change in rate of VF progression (i.e., standardized reduction per unit of IOP reduction of 0.840, calculated using changes in IOP and VF observed in the Canadian Glaucoma Study);[109] this was used to inform sensitivity analysis where the change in IOP resulted in slower disease progression than the reference-case analysis. In another scenario analysis, a faster rate of progression was modelled based on the reported decline in VF in untreated patients (i.e., –0.92 dB per year[110]).

The transition probabilities in each monthly cycle were estimated as the inverse of the number of months needed for a patient to transition from one health state to the next. For example, the average baseline VF in Model 1 was –6.65 dB (Table 8) and the numbers of months needed to transit from a moderate glaucoma stage to an advanced stage for two iStent Injects would therefore be calculated as:

$$\frac{(lower\ cutoff\ from\ next\ severeity\ stage - baseline\ IOP)}{annual\ rate\ of\ progression\ from\ treatment}$$
$$= (12 – 6.65) / 0.0177$$
$$= 364 \text{ months or } 30.2 \text{ years}$$

As such, the transition probability from moderate-to-advanced stage for iStent was 0.28% per month (the inverse of 364 months) or 3.3% per year.

Table 10: Relative Efficacy (Probability Distribution: Normal) of Reference-Case Models[a]

Model	Comparison	Baseline VF (dB)	IOP Reduction at 12 Months (mm Hg)	Medication Reduction at 12 Months	Reference (Type of Study)
Model 1: MIGS vs. pharmacotherapy	2x iStent Inject vs. Latanoprost + Timolol	NR	12.2 vs. 11.6 (*P* = NR)	NA	Fea et al., 2014 (RCT)[36]
Model 2: MIGS vs. laser therapy	Hydrus Microstent vs. SLT	–8.43 vs. –3.04	6.6 vs. 7.3 (*P* = 0.57)	1.4 vs. 0.5 (*P* < 0.01)	Fea et al., 2017 (prospective cohort)[62]
Model 3: MIGS vs. filtration surgery	Model 3a: Trabectome vs. Trabeculectomy with MMC	NR	10.7 vs 14.1 (*P* < 0.01); (6 mo) 4.4 vs. 15.1 (*P* = NR)	1.5 vs. 2.7 (*P* = NR); (6 mo) 0.28 vs. 1.82	Jea et al., 2012 (retrospective cohort);[64] Pahlitzsch et al., 2017 (prospective cohort)[25]
	Model 3b: ECP vs. Glaucoma Drainage Device (BGI or AGI)	–13.94 vs. –17.33	7.8 vs. 9.3 (*P* = NR); (24 mo) 14.07 vs. 14.73 (*P* = 0.7)	1.6 vs 1.5 (*P* = 0.74); (24 mo) 1 vs. 1 (*P* = NR)	Murakami et al., 2017 (retrospective cohort);[63] Lima et al., 2004 (non-radomized controlled trial)[61]
Model 4: MIGS + cataract surgery vs. cataract surgery alone	Hydrus Microstent + Phaco vs. Phaco alone	–3.61 vs. –3.61	Meta-analysis:[b] –0.8 (–1.4, –0.2) (*P* < 0.01)	Meta-analysis:[b] (24 mo) –0.41 (–0.56, –0.27) (*P* < 0.01)	Pfeiffer et al., 2015 (RCT);[71] Samuelson et al., 2018 (RCT)[88]
Model 5: MIGS + cataract surgery vs. filtration surgery + cataract surgery	Trabectome + Phaco vs. Trabeculotomy + Phaco	–11.6 vs. –15.38 NR	5.4 vs. 7.7 (*P* = 0.53) 2.7 vs. 6.4 (*P* = 0.35)	1.0 vs 1.6 (*P* = 0.027) 1.3 vs. 0.65 (*P* = 0.41)	Kinoshita-Nakano et al., 2018 (retrospective cohort);[85] Ting et al., 2018 (RCT)[87]

2x = two devices; AGI = Ahmed glaucoma implant; dB = decibels; BGI = Baeveldt glaucoma implant; ECP = endoscopic cyclophotcoagulation; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = month; NR = not reported; Phaco = phacoemulsification; RCT = randomized controlled study; SLT = selective laser trabeculoplasty; VF = visual field; vs. = versus.

Note: For comparisons 1 and 2, clinical studies were only available for iStent Inject and Hydrus Microstent. As such, other MIGS devices were not included in these comparisons.

[a] Details of clinical inputs evaluated in sensitivity analyses are presented in Table 44.

[b] Details on the meta-analysis are provided in Appendix 14.

These studies were selected as the reference case in each category of comparison based on the following criteria: a) when meta-analysis was available, the pooled clinical measure was used (Model 4); b) when a statistically significant difference (least conservative estimate) was observed in IOP reduction (Model 3a) or c) when 12-month data were reported (models 3b and 5). For Model 1, Fea et al. 2014 was selected as the reference case with the medication strategy assumed to entail two medications (i.e., average costs of one and three medication therapy). [36] Only one study was available for Model 2.[62] IOP reduction from the study was applied to the baseline rate of change (–0.6 dB per year and a standardized reduction of 0.905 for every unit of IOP) for each strategy. The remainder of the clinical studies were used to inform the range of relative efficacy that were examined in

probabilistic scenario analyses. Relative efficacy from different studies was standardized to 12-month rates to inform model inputs.

To account for the likelihood of attenuating relative efficacy over time, a 10% decline per year in the treatment effect of IOP reduction was assumed after the trial follow-up period for all interventions. Scenario analysis was undertaken assuming no treatment effect attenuation after trial follow-up period.

Relative medication reduction between two treatments was modelled, and the difference in medication use after 12-month follow-up was also assumed to decline 10% per year. For example, in Model 2, where the relative medication reduction at 12 months for Hydrus Microstent versus laser therapy was reported to be 1.4 versus 0.5 (i.e., 0.9 less for laser therapy), an incremental medication cost of 0.9 units was added to the laser therapy group.[62]

Drug adherence was only considered in Model 1. Adherence rate was not reported in either of the clinical studies available for medication versus MIGS.[36,58] As such, the reference case evaluated a range of adherence rates (20% to 95%) suggested by Newman-Casey et al.[111] The definition of "adherence" on treatment effects was based on a Canadian RCT that evaluated an educational intervention on glaucoma drug adherence and defined drug adherence as persistence of at least 75% of prescribed medication in one year.[112] Assuming similar definition of adherence (i.e., nonadherent patients are less than 75% adherent to their medication), and assuming there is a direct correlation between adherence and IOP reduction (i.e., nonadherent patients achieve 75% IOP reduction), the rate of disease progression for patients not adherent to medication was 25% faster than patients who demonstrated "complete" adherence. Furthermore, in a patient that is nonadherent, it was assumed that 75% of drug use (and cost) would be incurred.[112] Note that in the RCTs that inform relative efficacy, medication adherence was not reported; it was assumed that medication adherence in the RCTs represented "100%" adherence (reference case).

AEs from MIGS or surgical interventions were included in the model by applying a one-time AE-related cost and, for major complications or those necessitating a secondary surgical intervention, a disutility within the model's cycle in which the AEs were expected to occur. Prevalence of AEs was obtained from clinical studies (Table 11).

Table 11: Adverse Events in Reference-Case Models, Approach to Manage Different Types of Complications and Rates (> 2%)[a]

	Major Complications	Minor Complications	Secondary Surgical Interventions	Reference
Resources required to manage complications:	10% of major complications required minor eye interventions and two additional visits	Required two additional visits	Equal to minor eye interventions	Assumption per clinical expert feedback
Model 1: MIGS Vs. Pharmacotherapy				
2x iStent[b]	None reported	22%	NA	Vold et al. 2016[58]
Pharmacotherapy	None reported	17%	NA	
Model 2: MIGS Vs. Laser Therapy				
Hydrus Microstent	10%	16%	NA	Fea et al. 2017[62]
Laser therapy (SLT)	None reported	40%	NA	
Model 3a: MIGS Vs. Filtration Surgery				
Trabectome	None reported	4%	NA	Jea et al. 2012[64]
Trabeculectomy	13%	36%	NA	
Model 3b: MIGS Vs. Filtration Surgery				
ECP	12%	32%	NA	Lima et al. 2004[61]
Glaucoma Drainage device	26%	76%	NA	
Model 4: MIGS + Cataract Surgery Vs. Cataract Surgery				
Hydrus Microstent + Phaco	19%	18% to 35%	2%	Pfeiffer et al. 2015;[71] Samuelson et al. 2018[88]
Phaco-Emulsification	2%	18%	5%	
Model 5: MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery				
Trabectome + Phaco	NA	100%	None reported	Ting et al. 2018[87]
Trabeculectomy + Phaco	44%	99%	7%	Ting et al. 2018;[87] Marco et al., 2017[82]

2x = two devices; ECP = endoscopic cyclophotcoagulation; MIGS = minimally invasive glaucoma surgery; NA = not applicable; Phaco = phacoemulsification; SLT= selective laser trabeculoplasty.

[a] Further details available in Table 45, Appendix 15.

[b] Assumed rate of complications for iStent Inject would be similar to iStent.

Utilities

The baseline utility values for patients with glaucoma were derived from the formula developed by Van Gestel et al. in their discrete event simulation model:[113]

Health Utilities Index mark 3 = 0.88 – 0.101 * adverse events + 0.011 * VF – 0.065 * Cataract

The coefficients were derived from cross-sectional survey data collected on 531 Dutch patients with ocular hypertension or primary OAG and mapped the impact of VF loss, presence of cataracts, and development of side effects on utility values.[113] Utility estimates were based on the Health Utilities Index mark 3 using tariffs for the Canadian population. To estimate state-specific utility values, the midpoint VF in each health state (–3 dB for mild, –9 dB for moderate, –16 dB for advanced, and –26 dB for severe/blindness) was selected. Utility values were further specific to whether patients had cataract or no cataract (Table 12).

Disutility from side effects was assumed to be the same across all treatments in the model and was applied to one cycle within the model.

In the reference case, no disutility was applied to patients on medications. However, the Patients' Perspectives and Experiences Review has noted that patients find eye drops highly disruptive. As such, a disutility from medication was applied in a sensitivity analysis to explore how this may impact the cost-effectiveness of MIGS versus medication. In this sensitivity analysis, the side-effect coefficient (–0.101) from the previously used equation was applied to patients on medications.

Table 12: Utility Values Per Year for Health States

Variable Description	Base Estimate	Probability Distribution	Reference
Patients with Glaucoma without cataract		Beta	Van Gestel 2012[113]
Mild stage	0.847		
Moderate stage	0.781		
Advanced stage	0.704		
Severe/blindness	0.594		
With cataract			
Mild stage	0.782		
Moderate stage	0.716		
Advanced stage	0.639		
Severe/blindness	0.529		
Monthly disutility Trabeculectomy or complications requiring surgeries (one cycle)	0.008	Beta	Van Gestel 2012[113]

Costs

All costs were reported in Canadian dollars and, where appropriate, were inflated to 2018 costs using the Consumer Price Index for all items in Canada.[114]

MIGS device costs were obtained from a Canadian costing study[19] comparing MIGS with medications. For other device costs that were not listed in the literature, the clinical expert was consulted on this review to provide an estimate on these costs. Per the Implementation Issues Analysis review that noted start-up costs for MIGS are generally minimal or are covered by the manufacturers, it was assumed to be negligible.

Medication costs were updated using 2018 prices from Ontario[115] and Alberta[116] formularies (additional details are provided in Appendix 15). In Model 1, where MIGS was compared with medications, patients were assumed to be on two medications at baseline until subsequent treatment occured. The annual cost of one medication (Alberta: $96) was treated as the unit cost to calculate the cost of relative medication reduction for all models.

Surgeons' fees and OR costs were respectively obtained from the Schedule of Benefits and Ontario Case Costing Initiative (OCCI) (2016/2017 day surgery)[117] in Ontario, and Alberta Medical Association and Interactive Health Data Application[118] in Alberta to allow exploration of the potential variability in costs across Canada (and recognizing that specific billing fees for MIGS do not exist in many jurisdictions). Details on physician billing codes for each procedure are document in Table 47, Appendix 14.

In terms of OR costs for Trabeculectomy, it was assumed to be the same as those of a "major eye intervention" (OCCI 2016/17 day surgery[117]) given that, when converting the procedure code for Trabeculectomy to the Comprehensive Ambulatory Classification System grouper on the OCCI, it was equivalent to a major intervention. OR costs were not available for MIGS; these costs were estimated with reference to the OR costs of cataract surgery, and more specifically for phacoemulsification. The approach to estimate the OR cost were based on separating the proportion of phacoemulsification costs that represented fixed and variable costs. In particular, it has been suggested that OR for phacoemulsification consist of 51% fixed and 49% variable costs.[119] Fixed costs were assumed to be identical across all ophthalmological procedures while variable costs were adjusted according the time required to perform the procedure relative to the time required to perform phacoemulsification (approximately 20 minutes). The clinical expert consulted on this review provided insight to the expected procedure durations. Details of the calculation are presented in Table 13. To estimate the OR costs of combined surgeries (i.e., MIGS + cataract surgery or Trabeculectomy + cataract surgery), the variable cost for the second procedure was added to the overall OR cost of cataract surgery.

All secondary surgical interventions (i.e., subsequent Trabeculectomy) were assumed to require the same resource utilization.

Alberta costs (physician fees, OR, and medication) were used in the reference case analysis. Scenario analyses with Ontario costs were performed to explore the impact of a different province's health care service costs on the results.

Table 13: Detailed Calculation to Determine Operating Room Costs for MIGS or MIGS + Other Surgery

Alberta
OR cataract surgery cost (C060): $1,091 **Assumed to consist of:**[119] **51% fixed costs ($556)** **49% variable cost ($535)** Total time required to perform (according to clinical expert from the review): **Cataract surgery: 20 minutes** **MIGS: 10 (range: 4 to 18) minutes** **OR costs for MIGS-only:** **Assuming that the time to perform MIGS is 50% of cataract surgery, the variable costs would be calculated = $535 * 0.5 = $268** **OR MIGS cost = fixed cost + variable cost** **= $556 + $268** **= $824 ($663 – $984)** **OR costs for MIGS + cataract surgery:** **OR cataract surgery cost (C060): $1,091** **Variable cost for MIGS: $268** **Total cost for MIGS + Cataract Surgery = total costs of cataract surgery + variable costs of MIGS** **= $1,091 + $268** **= $1,359 ($1,198 – $1,519)** **OR costs for Trabeculectomy + cataract surgery:** **OR cataract surgery cost (C060): $1,091** **Variable cost for Trabeculectomy: 0.49 * $2,190 = $1,073**

Total cost for MIGS + cataract surgery = total costs of cataract surgery + variable costs of MIGS
= $1,091 + $1,073
= $2,164

Ontario

OR cataract surgery cost (C060): $714
Assumed to consist of:[119]
51% fixed costs ($364)
49% variable cost ($350)

Total time required to perform (according to clinical expert from the review):
Cataract surgery: 20 minutes
MIGS: 10 (range: 4 to 18) minutes

OR costs for MIGS-only:
Assuming that the time to perform MIGS is 50% of cataract surgery, the variable costs would be calculated = $350 * 0.5 = $175
OR MIGS cost = fixed cost + variable cost
= $364 + $175
= $539 ($434 – $644)

OR costs for MIGS + cataract surgery:
Ontario OR cataract surgery cost (C060): $714
Variable cost for MIGS: $175
Total cost for MIGS + cataract surgery = total costs of cataract surgery + variable costs of MIGS
= $714 + $175
= $889 ($784 – $994)

OR costs for Trabeculectomy + cataract surgery:
OR cataract surgery cost (C060): $714
Variable cost for Trabeculectomy: 0.49 * $1,560 = $764
Total cost for MIGS + cataract surgery = total costs of cataract surgery + variable costs of MIGS
= $714 + $764
= $1,478

MIGS = minimally invasive glaucoma surgery; OR = operating room.

Health state costs and utilization, including ophthalmologist consultations and set of tests including vision field test, optic disc imaging, and IOP measurement, were derived from Canadian Glaucoma Guidelines,[3] expert opinion, and Canadian sources (Table 14).[120,121] Ophthalmologist consultations are recommended at least every four to 12 months, depending on the stage of glaucoma severity. According to the Canadian guidelines, 1.5 sets of tests per year are further recommended for mild state, while two sets of tests are recommended for more severe diseases. Of note, in some jurisdictions, a maximum of two optic disc imagings per year are allowed for billing. Furthermore, one-time costs on low-vision aids (i.e., canes) were assumed to patients in the advanced stage.[122,123] Ongoing cost of low-vision services, including low-vision care specialist visits, non-Humphrey Visual Field testing and physical rehabilitation services were also applied to 25% patients in the severe/blind stage (Table 14).[121,124]

In terms of costing for AEs, the model assumed two additional ophthalmologist consultations for any AEs, and 10% of major complications would require surgical intervention, which was assumed to be equivalent to the cost of minor eye intervention and a physician fee equivalent to paracentesis.

Table 14: Cost Parameters Used in the Model (2018 Canadian Dollars)

Variable Description	Costs Range	Reference-Case Value ($)	Probability Distribution	Reference
MIGS (device) iStent/iStent Inject 2x iStent/2xiStent Inject ECP Trabectome XEN45 Hydrus Microstent CyPass Micro-Stent	 500 (2011 $) 1,000 (assumed double of iStent/iStent Inject) 200 (2011 $) 700 (2011 $) Same as 2x iStent Same as 2x iStent 1,150	 543.5 1,087 218 761 1,087 1,087 1,150	 Gamma (+/–25%)	 Iordanous[19] Expert opinion
Pharmacotherapy (annual) 1 med 2 meds 3 meds	 101 (ON); 96 (AB) 230 (ON); 219 (AB) 320 (ON); 294 (AB)	 96 219 294	 Gamma (1 to 3 meds in Model 1)	Iordanous,[19] ON[115] and AB formulary[116] (additional details in Appendix 15)
Drainage Device Ahmed valve	 926.5	 927		 Expert opinion
Surgeons' fees[a] Trabeculectomy Ab-interno[b] (iStent, Trabectome) SLT Drainage surgery Cataract surgery only MIGS + cataract surgery Trabeculectomy + cataract surgery	 655 (ON); 1,245 (AB) 550 to 840 (ON); 469 (AB) 206 (ON); 417 (AB) 945 (ON); 1,594 (AB) 398 (ON); 408 (AB) 822 to 1,112 (ON); 775 (AB) 927 (ON); 1,552 (AB)	 1,245 469 417 1,594 408 775 1,552	 Gamma for MIGS	 Expert opinion SOB[120], AMA[125] (additional details in Appendix 15)
Operating room[c] Trabeculectomy MIGS SLT Cataract surgery only Major intervention Minor intervention MIGS + cataract surgery Trabeculectomy + cataract surgery	 Equal to "major intervention" (see below) 539 (ON); 824 (AB) 468 (ON); 146 (AB) 714 (ON); 1,091 (AB) 1,560 (ON); 2,190 (AB) 403 (AB); 999 (ON) 889 (ON); 1,358 (AB) 1,478 (ON); 2,164 (AB)	 2,190 824 146 1,091 2,190 403 1,358 2,164	 Gamma for MIGS	 OCCI,[117] IHDA [118] Phaco (C060), major eye intervention (C056); minor eye intervention (C057); SLT (C062)
Post-operative visits (n)[d] Trabeculectomy (8) iStent (7) SLT (1) XEN (8) Cataract surgery (2)	 285 (ON); 402 (AB) 256 (ON); 357 (AB) 82 (ON/AB) 285 (ON); 402 (AB) 111 (ON); 128 (AB)	 402 357 82 402 128		 SOB[120], AMA[125] ON: A235 + A234 AB: 03.03A + CMGP02 + 03.03A
Annual health state–related Mild stage: 1 visit and 1.5 sets of tests[e] Moderate stage: 2 visits and 2 sets of tests Advanced stage: 3 visits, 2 set of	 198 (ON); 284 (AB) 267 (ON); 397 (AB) 296 (ON); 443 (AB)	 284 397 443		 SOB[120], AMA[125] Lee et al. 2006[121] (additional details in Appendix 15)

Variable Description	Costs Range	Reference-Case Value ($)	Probability Distribution	Reference
tests and one-time low-vision aid (cane) Severe/blindness: 4 visits, 2 set of tests and low-vision services for 25% patients (US 2006 $511)	(+24) 325 (ON); 489 (AB) (+173)	(+24) 489 (+173)		
Complications Minor intervention Surgeon's fees (assumed paracentesis) 2 follow-up visits	999 (ON); 403 (AB) 70 (ON); 55 (AB) 111 (ON); 128 (AB)	403 55 128		OCCI,[117] IHDA[118] Minor intervention (C057); SOB[120] paracentesis (ON: Z851; AB: 66.91A).
Subsequent treatments Trabeculectomy	1,560 (ON); 2,190 (AB)	2,190		OCCI,[117] IHDA[118]

2x = two devices; AB = Alberta; AMA = Alberta Medication Association; CMG = case mix group; ECP = endoscopic cyclophotocoagulation; IHDA = Interactive Health Data Application (AB); MIGS = minimally invasive glaucoma surgery; OCCI = Ontario case costing initiative; ON = Ontario; Phaco = phacoemulsification; SLT= selective laser trabeculoplast; SOB = Schedule of Benefit (ON).

[a] Included anesthetics and surgical assistant and time costs (assumed 30 min); codes provided in Appendix 15.

[b] Assumed E132 or E136 code for ab interno procedures in ON.

[c] Included direct (nursing, diagnostic imaging, medication, and laboratory services) and overhead expense.

[d] Post-op visits in the first three months were modelled as part of the initial cost of the intervention; combo surgery (MIGS + Phaco or Trabeculectomy + Phaco) were assumed to occur within the same visits as MIGS and Trabeculectomy, respectively.

[e] Test consisted of the following: vision field test, optic disc imaging, and intraocular pressure measurement.

4.1.6 Sensitivity Analysis and Scenario Analysis

The reference case reflects the probabilistic results based on 1,000 Monte Carlo simulations. The probabilistic results characterize the extent to which parameter uncertainty affects the cost-effectiveness estimates in the model. Standard distributional forms were taken to describe the probability distribution functions relating to input parameters: relative efficacy (relative IOP reduction and relative medication reduction) were characterized by normal distributions, utility and complication rates were characterized by beta distribution, and costs were characterized by gamma distributions. Details on the probabilistic values within each model can be found in Table 49. Probabilistic scenario analyses were further performed to explore uncertainties in specific model inputs or to address known variability in clinical practices. The ranges of plausible values for model parameters were tested in the base-case probabilistic models, and distributions were informed by the reference case or meta-analysis for that comparison (additional details in Appendix 15). Cost-effectiveness acceptability curves demonstrating the probability that a modality would be considered optimal at a given WTP threshold were also presented.

As noted, the specific MIGS device selected for the reference case differed by model based on the available clinical evidence from the Clinical Review (Table 10). Specifically, for models 3a and 4, in which more than two different MIGS devices have been studied and in which the necessary clinical outcome data were available, non–reference-case analyses were conducted for the other MIGS devices that had not been selected for the reference-case. This involved adjusting the effectiveness on IOP and applying the specific device cost to explore the plausible range of ICURs associated with different MIGS devices for that specific comparison.

Across all five models, the following sensitivity analyses were performed:

1. one-year time horizon
2. lifetime horizon with no treatment effect on reduction in IOP and no reduction in medication use after one year (except for Model 1, when only IOP was modelled)
3. no relative treatment effects when clinical results were not statistically significant ([A] one-year and [B] lifetime) and no other clinical studies were available
4. discount rates of (A) 0% and (B) 5%
5. Ontario costing data (A) drug markup costs applied, and (B) proposed $400 physician billing fees for MIGS in Ontario. A summary of how the cost inputs differ between Alberta and Ontario can be found in Table 15
6. no subsequent treatment with Trabeculectomy if VF progress to < –12dB for models 1 to 3a, and 4
7. faster progression of VF loss in untreated patients (–0.92 per year[110])
8. slower progression of VF loss for every unit of IOP reduction (i.e., reduction factor of 0.84).[109]

Specific to Model 1 only, the following additional sensitivity analyses were performed:

1. inclusion of the cost of drug markup and dispensing fees
2. drug adherence ranging from 20% to 95%. Furthermore, the impact of nonadherence to treatment was varied by two approaches:
   a. nonadherent patients would have medication costs and treatment effectiveness reduced by 75%
   b. nonadherent patients would have no reduction in medication costs and derive no effectiveness (no IOP reduction) (most conservative scenario)
3. disutility for patients on medication:
   a. an annual disutility of 0.101[113] was applied to all patients on medications
   b. an annual disutility of 0.101[113] was applied to only patients who were adherent to medication.

Table 15: Comparison of Total Intervention Cost Between Alberta and Ontario (2018 Canadian Dollar)[a]

Variable Description	AB Total Costs ($)	ON Total Costs ($)
Model 1: MIGS Vs. Pharmacotherapy		
MIGS	2,737	2,432 to 2,722
Pharmacotherapy (annual)	96 to 294	101 to 320
Model 2: MIGS Vs. Laser Therapy		
MIGS	2,737	2,432 to 2,722
Laser therapy	645	756
Model 3: MIGS Vs. Filtration Surgery		
Trabectome ECP 2x iStent XEN45	2,411 1,868 2,737 2,737	2,106 to 2,396 1,563 to 1,853 2,432 to 2,722 2,432 to 2,722
Filtration Surgery	3,837 to 5,113	2,500 to 3,717
Model 4: MIGS + Cataract Surgery Vs. Cataract Surgery		
Hydrus Microstent + cataract surgery 2x iStent + cataract surgery ECP + cataract surgery CyPass Micro-Stent + cataract surgery	3,577 3,640 2,708 3,640	3,054 to 3,344 3,117 to 3,417 2,185 to 2,475 3,117 to 3,407
Cataract surgery alone	1,627	1,123
Model 5: MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery		
MIGS + cataract surgery	3,251	2,728 to 3,018
Filtration surgery + cataract surgery	4,118	2,690

2x = two devices; AB = Alberta; ECP = endoscopic cyclophotocoagulation; MIGS = minimally invasive glaucoma surgery; ON = Ontario; vs. = versus.

[a] Includes device costs (when applicable), surgeon's fees, operating room, and post-operative visits. Details listed in Table 14.

4.1.7 Model Validation

The model structure and data inputs were presented to the clinical experts to ensure that the model, its parameters, and its assumptions reflect clinical practice and the available body of literature (i.e., face validity). Internal validity was assessed through a peer review process to ensure the mathematical calculations were performed correctly and were consistent with the model specification.

4.1.8 Assumptions

The reference-case analysis was developed according to the following key assumptions:

- Patients experience a constant rate of glaucoma progression, regardless of glaucoma severity. This assumption was tested in sensitivity analysis, where late-stage glaucoma progresses at a faster rate.
- It was assumed that there would be no treatment- or condition-related mortality effects. Differences in QALYs between strategies therefore reflect differences in disease progression or side-effect profile between treatment strategies.
- Treatment effects of IOP and medication reduction were measured at 12 months (time point where most RCTs reported clinical outcomes per the Clinical Review) and

converted into monthly rates to reflect the model's monthly cycle. A 10% decline in the treatment effect on IOP after 12 months was assumed in the model.

- Progression of VF loss was estimated through the association of the change in IOP and VF progression, and this association was assumed to be monotonic throughout the spectrum of baseline IOP and VF.
- It was assumed that the relative efficacy of treatment would be similar regardless of disease severity (defined by VF).
- Cost, IOP reduction, and complications were modelled for subsequent treatment (Trabeculectomy). However, relative medication reduction was the same across treatment groups.
- Indirect health consequences, such as falls, were not considered.
- For major complications or those necessitating a secondary surgical intervention, a one-time disutility of –0.008 was applied.
- The costs of minor complications for medications were assumed to last for one month like other interventions, instead of being continuously incurred. This may provide a slight underestimation of the expected costs associated with medication.

4.2 Results

4.2.1 Analysis

Reference-Case Analysis

The results of the probabilistic reference case for each model are presented in Table 16; demonstrating lifetime expected costs and QALYs, incremental costs and QALYs, as well as the ICUR. Disaggregated lifetime costs from a deterministic analysis are further presented in Table 17. Of note, each model considered a different set of comparators, and may consider different patient populations (Table 8). As such, comparisons of results between models are not appropriate.

Nonetheless, several overarching findings are present across all five models. First, the lifetime total cost per patient for glaucoma and treatment ranged between $8,431 and $14,621, depending on the treatment strategy and patient's baseline disease severity. By cost categories, the costs of disease management made up the largest amount of costs (Table 17), with intervention costs being the next most costly. Across the five models, the incremental QALYs between comparators ranged between 0.023 and 0.070, which equated to a difference of approximately eight to 25 days of additional "perfect" health over a lifetime.

Table 16: Lifetime Probabilistic Analysis: Reference Case

Category	Costs ($)	QALYs	Incremental Cost ($) MIGS Vs. Comparator	Incremental QALYs MIGS Vs. Comparator	ICUR ($/QALY)
Model 1: Pharmacotherapy MIGS	 11,900 12,641	 12.85 12.89	 741	 0.039	 MIGS (vs. medication): 18,808
Model 2: Laser therapy MIGS	 9,013 10,739	 10.36 10.34	 1,726	 –0.023	 MIGS dominated (more expensive, less effective)
Model 3a (moderate stage): MIGS Filtration surgery	 12,672 13,375	 12.42 12.49	 –703	 –0.070	 Filtration surgery (vs. MIGS): 10,093
Model 3b (advanced stage): MIGS Filtration surgery	 11,354 14,621	 10.83 10.85	 –3,267	 –0.027	 Filtration Surgery (vs. MIGS): 121,959
Model 4: Cataract surgery alone MIGS + cataract surgery	 8,431 10,072	 9.04 9.06	 1,641	 0.026	 MIGS + Phaco (vs. Phaco alone): 63,626
Model 5: MIGS + cataract surgery Filtration surgery + cataract surgery	 10,836 11,309	 7.89 7.92	 –473	 –0.032	 Filtration surgery + Phaco (vs. MIGS + Phaco): 14,968

ICUR = incremental cost-utility ratio; MIGS = minimally invasive glaucoma surgery; Phaco = phacoemulsification; QALYS = quality-adjusted life-years; vs. = versus.

Table 17: Disaggregated Lifetime Costs, by Cost Categories (Deterministic Results)

Cost Categories, By Intervention	Costs ($)					
	Model 1: MIGS Vs. Pharmacotherapy	**Model 2: MIGS Vs. Laser Therapy**	**Model 3a: MIGS Vs. Filtration Surgery (Moderate Glaucoma)**	**Model 3b: MIGS Vs. Filtration Surgery (Advanced Glaucoma)**	**Model 4: MIGS + Cataract Surgery Vs. Cataract Surgery Alone**	**Model 5: MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery**
MIGS (total[a])	**12,641**	**10,723**	**12,613**	**11,397**	**10,072**	**10,772**
Intervention	2,380	2,380	2,054	1,511	3,219	2,894
Complications	28	38	5	62	56	128
Post-op visits	357	357	357	357	357	357
State-related	9,876	7,948	9,595	9,535	6,440	7,024
Add med[b]	NA	0	602	–68[c]	0	369
Comparator (total[a])	**11,903**	**9,017**	**13,284**	**14,572**	**8,423**	**11,245**
Intervention	1,886	563	3,435	4,711	1,499	3,716
Complications	22	51	69	142	55	203
Post-op visits	0	82	402	402	128	402
State-related	9,995	7,889	9,378	9,317	6,527	6,924
Add med[b]	NA	432	0	0	214	0

Add med = additional medication; MIGS = minimally invasive glaucoma surgery; NA = not applicable; vs = versus.

[a] Total costs presented here differ slightly from those reported in the probabilistic analyses in Table 16 because these reflect deterministic estimates.

[b] As described in the methods, medication costs were only applied to one comparator group with the other group (i.e., reference) set at 0.

[c] To keep the consistency between models 3a and 3b, incremental medication costs were added to the MIGS arm. In model 3b, medication reductions for MIGS were larger than for filtration surgery; as such the incremental medication costs were negative, implying a cost saving.

The detailed results and sensitivity analyses by each model are subsequently presented. Further, detailed results of the probabilistic results on the incremental cost-effectiveness plane can be found in Appendix 16.

Model 1: MIGS Versus Pharmacotherapy (Baseline at Moderate Glaucoma)

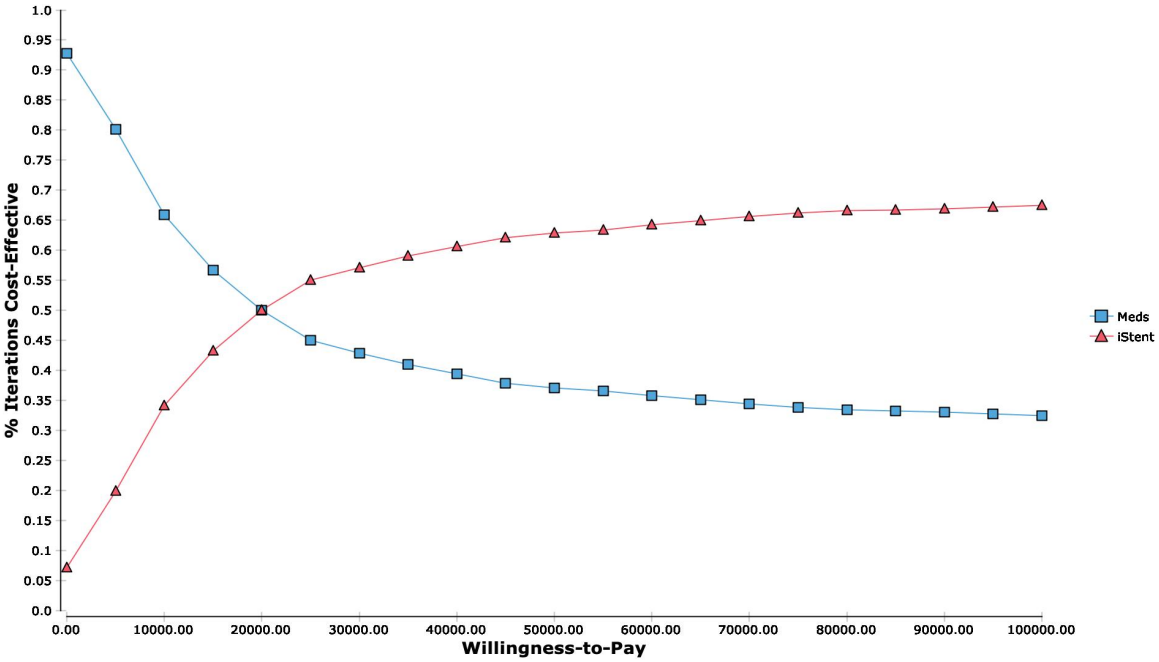
Reference Case and Cost-Effectiveness Acceptability Curve

As the Clinical Review only found clinical studies that have compared iStent Inject (2nd generation) to pharmacotherapy, the findings below specifically address the cost-effectiveness of iStent compared with pharmacotherapy. The potential cost-effectiveness of other MIGS devices to a pharmacotherapy strategy remains unclear and could not be explored in the Economic Evaluation.

Over a lifetime horizon in patients with moderate glaucoma, MIGS was associated with an additional $741 in costs, but provided an additional 0.039 QALYs, leading to an ICUR of $18,808 per QALY compared with a pharmacotherapy-based treatment strategy (Table 16). Intervention costs were similar between strategies ($2,380 versus $1,886), although the timing in which costs would be incurred differed. In the MIGS strategy, treatment-related costs occurred at the start of the model due to the high up-front costs associated with surgery, whereas treatment-related costs were constantly incurred in the pharmacotherapy strategy through the model's time horizon. At lower WTP thresholds, pharmacotherapy was favoured; however, at willingness-to pay thresholds of $18,808 per QALY and above, MIGS was favoured (Figure 9). At a WTP threshold of $50,000 per QALY or $100,000 per QALY, the probability that MIGS was the most likely preferable strategy compared with

pharmacotherapy was approximately 60% and 65%, respectively (similar from the Ontario setting, Figure 10). This underscores the uncertainty inherent in this comparison.

Figure 9: Cost-Effectiveness Acceptability Curve for Model 1 (iStent Inject Versus Pharmacotherapy): Reference Case



meds = medications.

Sensitivity Analyses

In sensitivity analyses, Model 1 was highly sensitive to changes that impacted clinical effectiveness estimates (Table 18). For instance, if assuming that there was no difference in clinical effectiveness between MIGS and pharmacotherapy after 12 months or in adopting a one-year time frame, the ICURs ranged between approximately $291,000 and $9.4 million per QALY gained. The instability in the ICUR was largely due to the very small difference in QALYs that would be estimated in these scenarios as the incremental treatment benefits would accrue only in the first year of treatment.

Adherence with medication, as well as disutility to medication use, also impacted the results. The larger the proportion of patients who were nonadherent, the more favourable MIGS procedure appeared as patients who were nonadherent were assumed to have worse clinical outcomes. The disutility associated with medication use, as estimated by Van Gestel, also had a significant impact on effectiveness, with MIGS appearing more attractive, although from a face validity perspective, the disutility from this source (–0.10 [i.e., assumes patients are willing to forego 10% of their time alive to avoid medication use]) was very large.

Arguably, an alternate reference case would be to assume no difference in IOP between comparators given that no statistical analysis was conducted to compare between treatment groups among the included clinical studies identified from the Clinical Review. This non-reference-case analysis assumed identical efficacy between MIGS and pharmacotherapy

with the safety profile driving the clinical differences observed between these two interventions. The incremental QALYs between these two treatment strategies were therefore smaller in this scenario, leading to ICURs that were slightly higher than the reference case (ICUR of $27,770 versus $18,808 respectively) (Table 18).

In addition, the model was sensitive to treatment-related costs. When medication costs included markup (7%) and dispensing fees ($12 per bottle), over a lifetime time horizon, MIGS appeared to be cost savings compared with pharmacotherapy. If Ontario costs were used, with a proposed $400 physician billing fee to perform a MIGS procedure (lower than the physician billing costs from Alberta that informed the reference case), the ICUR lowered to $5,173 per QALY gained. MIGS also became the dominant strategy (i.e., MIGS was less costly and more effective) when markup (8%) and dispensing fees (approximately $9 per bottle) were added to the medication costs under an Ontario setting (Table 18).

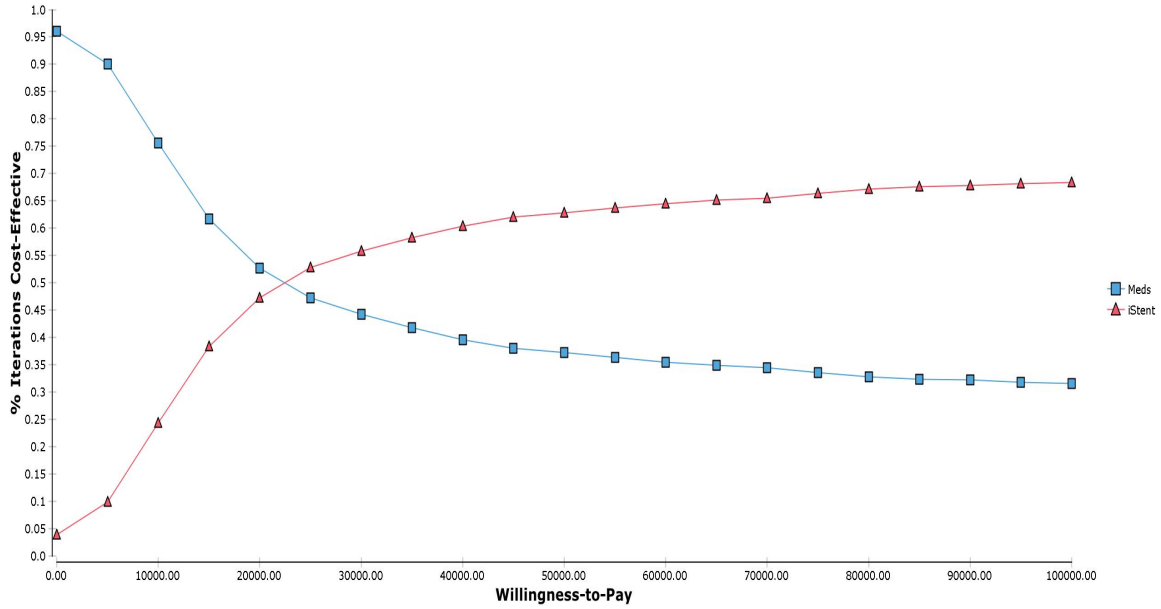
Table 18: Sensitivity Analyses, Probabilistic (Model 1: MIGS Versus Pharmacotherapy)

Category	Incremental Costs ($) MIGS Vs. Pharmacotherapy	Incremental QALYs MIGS Vs. Pharmacotherapy	ICUR of MIGS Vs. Pharmacotherapy ($/QALY)
Reference case	**741**	**0.039**	**18,808**
Sensitivity Analyses			
1. One year	2,508	0.0003	9,409,141
2. No effect after 12 Months	1,279	0.004	291,099
3A. Assumed same IOP between strategies (lifetime)	763	0.027	27,770
3B. Assumed same IOP between strategies (one-year horizon)	2,517	0.0002	12,299,882
4A. 0% discount rate	510	0.051	9,963
4B. 5% discount rate	1,129	0.025	45,373
6. No subsequent treatment with filtration surgery	794	0.054	14,601
7. Faster baseline VF progression (–0.92 dB annual progression)	1,086	0.049	22,267
8. Slower disease progression per unit of IOP reduction (from Canadian Glaucoma Study)	726	0.041	17,648
10. AB cost with drug markup (7%) and dispensing fees ($12.15 per bottle)	–537	0.039	MIGS dominant (less expensive, more effective)
11. Complete adherence	554	0.013	41,375
11A. 95% adherence	562	0.013	42,771
11B. 20% adherence	900	0.063	14,239
Range of adherence (20-95%) with full medication cost and no IOP reduction (d)	457	0.128	3,565
12A.Disutility to all patients on medications	748	1.006	744
12B. Disutility to adherent patients on medications	755	0.592	1,275
5. Ontario Setting			
ON cost inputs (combined billing)	552	0.039	14,120
ON cost inputs (less intensive billing)	375	0.041	9,093
ON cost inputs (more intensive billing)	655	0.040	16,488

Category	Incremental Costs ($) MIGS Vs. Pharmacotherapy	Incremental QALYs MIGS Vs. Pharmacotherapy	ICUR of MIGS Vs. Pharmacotherapy ($/QALY)
ON cost inputs (proposed $400 physician fee code for MIGS)	198	0.038	5,173
ON cost with drug markup (8%) and dispensing fees ($8.83 per bottle)	–440	0.038	MIGS dominant (less expensive, more effective)

AB = Alberta; dB = decibels; ICUR = incremental cost-utility ratio; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; ON = Ontario; QALYs = quality-adjusted life-years; VF = visual field.

Figure 10: Cost-Effectiveness Acceptability Curve for Model 1 (iStent Inject Versus Pharmacotherapy): Ontario Setting Assuming Combined Billing



meds = medications.

Interpretation

There are significant areas of uncertainty that preclude definitive conclusions on the optimal treatment strategy for MIGS versus pharmacotherapy. As in all models, the limitations of the underlying clinical efficacy data (surrogate outcomes, short-term follow-up, small number of studies) should be considered. As noted, for this pairwise comparison, only iStent and iStent Inject have been studied in a clinical trial setting, and the economic analysis specifically focused on iStent Inject. The costs associated with MIGS were estimated given that detailed Canadian micro-costing data are lacking, as are specific physician billing codes in many Canadian jurisdictions. Sensitivity analyses highlighted the fact that the cost of MIGS plays a key role in determining its potential cost-effectiveness, and further assessment of actual costs would be valuable as plausible scenarios suggest that there are conditions where MIGS may be cost neutral or even cost saving. Finally, the side effects of medication and adherence are important factors to consider. The reference case assumed that no medication-specific disutilities and incorporated Canadian-reported adherence rates for medication use. However, sensitivity analyses highlighted the fact that, if more conservative

assumptions were selected for the pharmacotherapy strategy (e.g., lower drug adherence or disutility applied to being on medication), MIGS may be an attractive treatment option in such populations whereby adherence to medication is expected to be low or if there are considerable side effects experienced on medication.

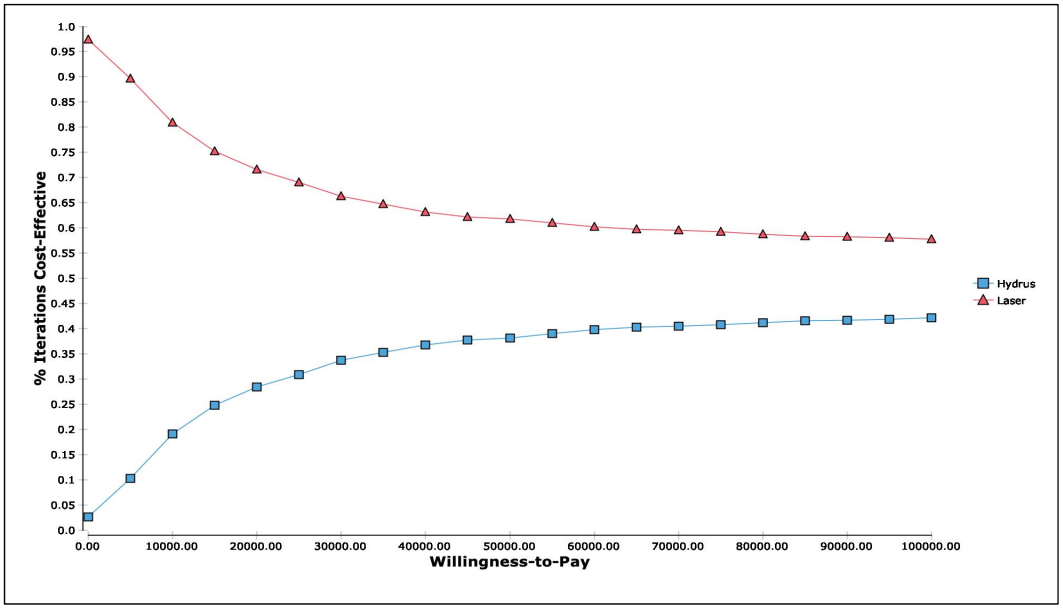
Model 2: MIGS Versus Laser Therapy (Baseline at Mild Glaucoma)

Reference Case and Cost-effectiveness Acceptability Curve

Similar to Model 1, only one type of MIGS has been directly studied clinically in this comparison between MIGS and laser therapy. Specifically, the Clinical Review identified one clinical study[62] that compared Hydrus Microstent with laser therapy (i.e., SLT). As such, the findings below specifically address the cost-effectiveness of Hydrus Microstent compared with SLT and the potential cost-effectiveness of other MIGS devices remains unclear and could not be further explored given the lack of comparative clinical data.

In the reference case, MIGS was associated with additional costs of $1,726, but fewer QALYs (–0.023) than laser therapy. MIGS was therefore dominated by laser therapy (i.e., laser therapy was more effective and less costly) (Table 16). These findings were due to the fact that no significant difference in IOP reduction was noted between Hydrus Microstent and laser therapy groups within the clinical study (see Clinical Review) and, while health state costs were similar between the two comparators (Table 17), the treatment-related costs for MIGS were considerably larger than for laser therapy ($2,380 versus $563) and were not offset by cost savings from reduced medication. The cost-effectiveness acceptability curve (Figure 11) shows that laser therapy was preferred across all WTP thresholds and, at a WTP threshold of $50,000 per QALY, the probability that laser therapy was preferred to MIGS was between 60% and 65%.

Figure 11: Cost-Effectiveness Acceptability Curve for Model 2 (Hydrus Microstent Versus Laser Therapy): Reference Case



Hydrus = Hydrus Microsent.

Sensitivity Analyses

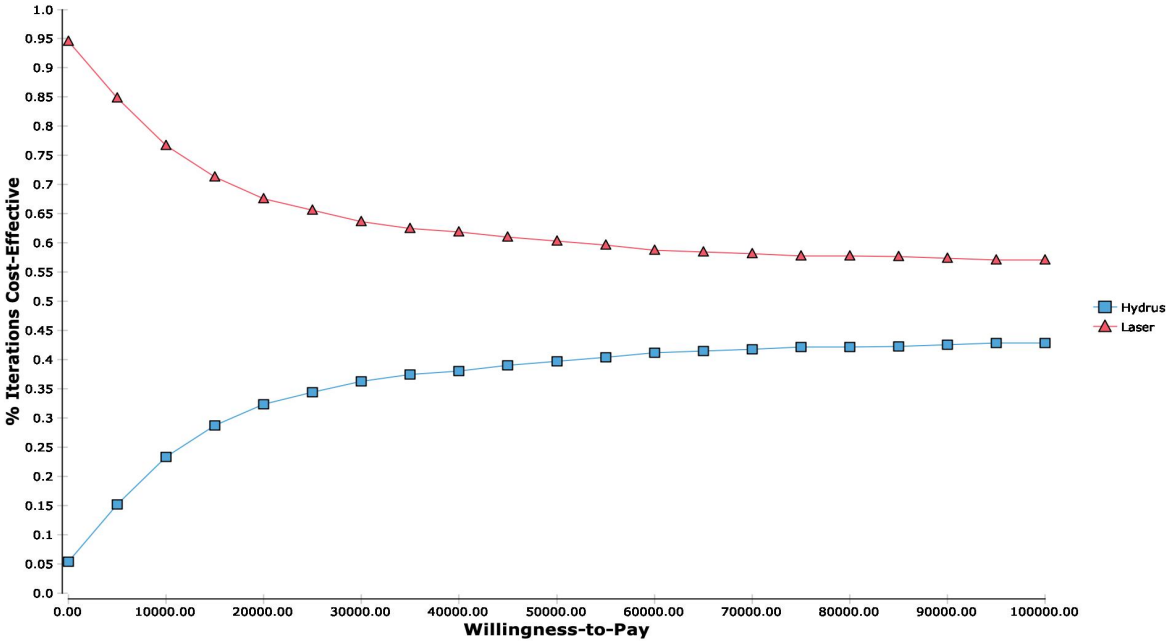
Across the range of sensitivity analyses performed, the model remained robust as laser therapy remained the dominant strategy (Table 19). Although there were differences in incremental QALYs observed across sensitivity analyses, a strategy consisting of MIGS always remained more costly than laser therapy. As the only clinical study identified in the review did not reveal a statistically significant difference in change in IOP, a non-reference-case analysis was conducted that assumed no difference in IOP between the two comparators. Under this analysis, the expected QALYs observed were similar between strategies with a QALY difference of less than 0.0004.

Table 19: Sensitivity Analysis, Probabilistic (Model 2: MIGS Versus Laser Therapy)

Category	Incremental Costs($) MIGS Vs. Comparator	Incremental QALYs MIGS Vs. Comparator	ICUR of MIGS Vs. Laser Therapy ($/QALY)
Reference case	**1,726**	**–0.023**	**MIGS Dominated (more expensive, less effective)**
Sensitivity Analyses			
1. One year	2,025	–0.001	Dominated (more expensive, less effective)
2. No effect after 12 months	2,055	–0.006	Dominated (more expensive, similarly effective)
3A. Assumed same IOP between strategies (lifetime)	1,645	–0.0004	Dominated (more expensive, similarly effective)
3B. Assumed same IOP between strategies (one year)	2,003	–0.0004	Dominated (more expensive, similarly effective)
4A. 0% discount rate	1,694	–0.032	Dominated (more expensive, similarly effective)
4B. 5% discount rate	1,831	–0.028	Dominated (more expensive, similarly effective)
6. No subsequent treatment with filtration surgery	1,742	–0.063	Dominated (more expensive, similarly effective)
7. Faster baseline VF progression (–0.92 dB annual progression)	1,729	–0.021	Dominated (more expensive, similarly effective)
8. Slower disease progression per unit of IOP reduction (from Canadian Glaucoma Study)	1,669	–0.018	Dominated (more expensive, similarly effective)
5. Ontario Setting			
ON costs inputs (combined billing)	1,377	–0.027	Dominated (more expensive, similarly effective)
ON cost inputs (less intensive billing)	1,263	–0.021	Dominated (more expensive, similarly effective)
ON cost inputs (more intensive billing)	1,616	–0.030	Dominated (more expensive, similarly effective)
ON cost and proposed $400 physician fees for MIGS	1,101	–0.029	Dominated (more expensive, similarly effective)

dB = decibels; ICUR = incremental cost-utility ratio; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; ON = Ontario; QALYs = quality-adjusted life-years; VF = visual field.

Figure 12: Cost-Effectiveness Acceptability Curve for Model 2 (Hydrus Microstent Versus Laser Therapy): Ontario Setting Assuming Combined Billing



Hydrus = Hydrus Microstent.

Interpretation

While there is uncertainty regarding the true relative effectiveness of MIGS and laser therapy, the currently available data from one study[62] suggested that there was no difference in clinical efficacy with respect to IOP reduction. At current procedure cost estimates, laser therapy strategy was overall less costly even when accounting for the additional medication costs that would be required for laser therapy, reflecting the difference in medication use reported in the clinical study. This finding did not change even when lower cost estimates for MIGS were used based on Ontario billing codes (sensitivity analysis 5). Laser therapy was found to be the preferred strategy across all sensitivity analyses performed.

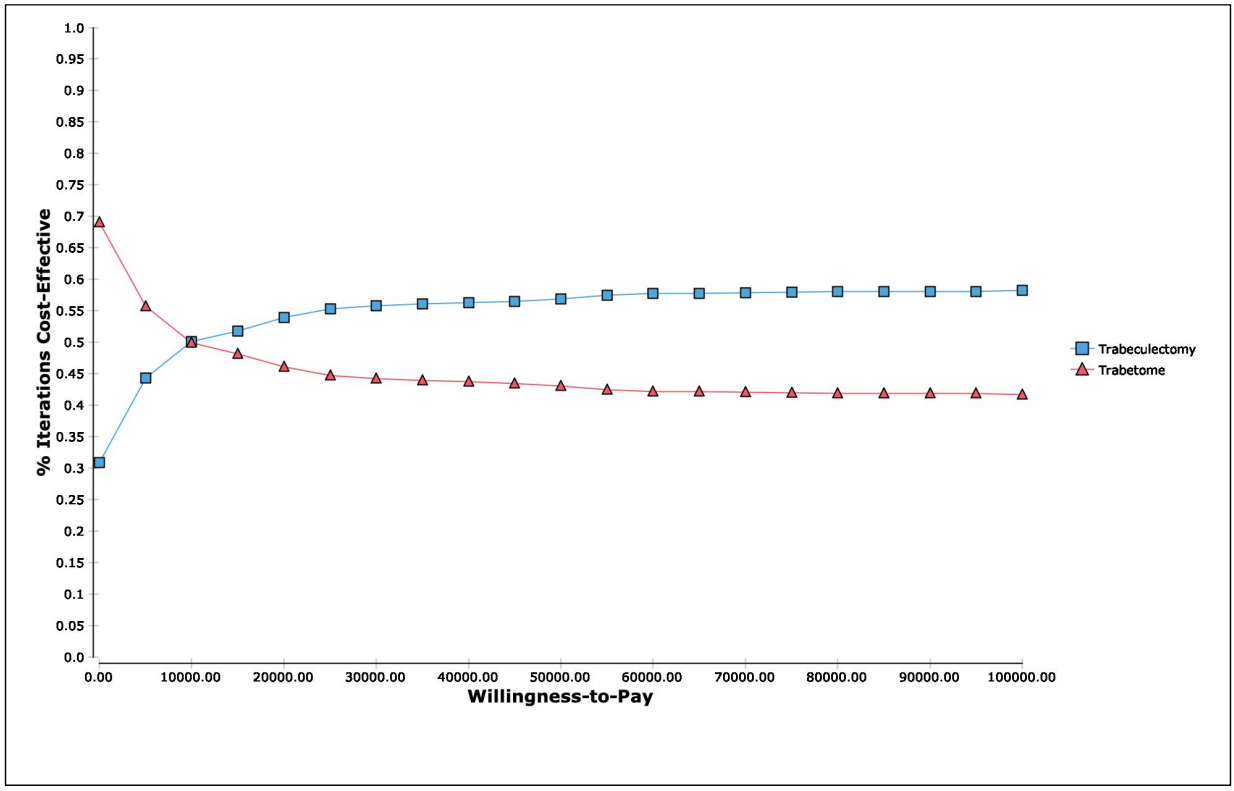
Model 3: MIGS Versus Filtration Surgery (Baseline at Moderate-to-Advanced Glaucoma)

Reference Case and Cost-effectiveness Acceptability Curve

Models 3a and 3b examined a cohort of patients with either moderate- or advanced-stage glaucoma. MIGS was less costly than filtration surgery; however, it was also less effective. In other words, filtration surgery was found to be more expensive and more effective over a patient's lifetime and the ICURs of filtration surgery compared with MIGS are shown in Table 16. In both submodels, the primary driver in cost between strategies was the intervention-related costs (Table 17).

The reference case for model 3a (patients with moderate-stage disease) was based on the clinical study by Jea et al[64] that compared Trabectome with Trabeculectomy with mitomycin C. Based on this study, the incremental cost of filtration surgery was found to be $703 and the additional benefits was 0.070 QALYs compared with MIGS, leading to an ICUR of $10,093 per QALY gained for filtration surgery versus MIGS (Table 16). The cost-effectiveness acceptability curve indicated that filtration surgery was preferred except when the WTP threshold was less than $10,000 per QALY. Above this value, the probability that filtration surgery was preferred ranged from 50% to 60% and, similar to Model 1, this highlighted the considerable parameter uncertainty to this analysis (Figure 13).

Figure 13: Cost-Effectiveness Acceptability Curve for Model 3a (MIGS Versus Surgery; Moderate Stage): Reference Case



MIGS = minimally invasive glaucoma surgery.

Other clinical studies were identified from the Clinical Review on other MIGS devices for this pairwise comparison. The relative efficacy and safety inputs reported in these studies and the device-specific costs were used to inform the possible range in cost-effectiveness of different MIGS devices. The analysis highlighted the wide uncertainty associated with the economic findings for this pairwise comparison. Although MIGS produced fewer QALYs over a lifetime compared with filtration surgery (in alignment with the Clinical Review findings), the cost difference of MIGS ranged from being more to less costly compared with filtration surgery. As such, the potential cost-effectiveness of different MIGS devices ranged from dominated to being cost-effective compared with filtration surgery depending on the expected cost difference between these treatment strategies (Table 20).

Table 20: Range of Cost-Effectiveness of MIGS Versus Filtration Surgery, by Different MIGS Devices[a]

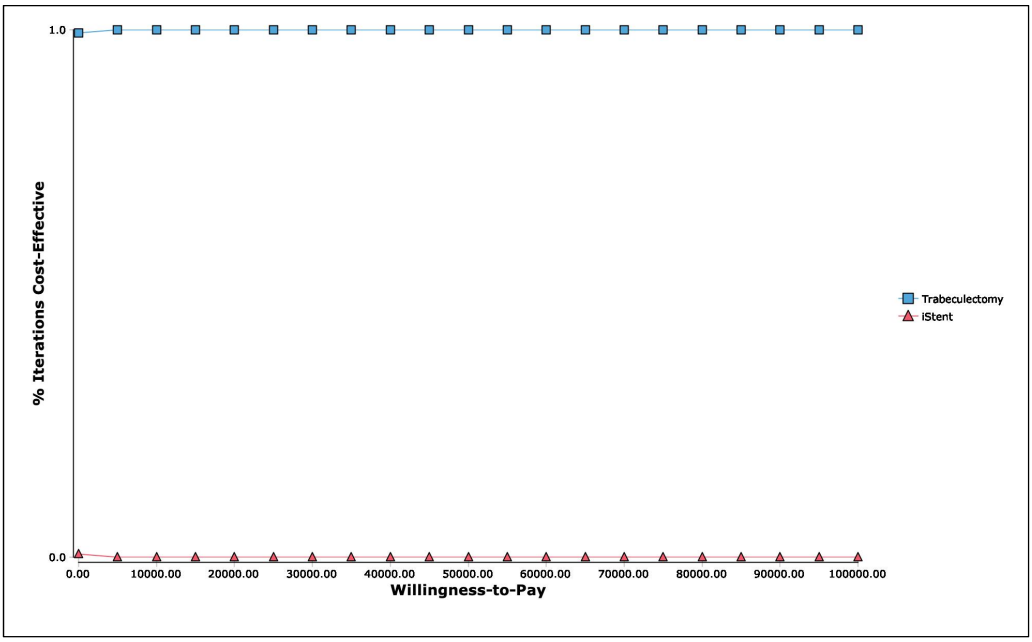
Category	Incremental Cost ($) MIGS Vs. Comparator	Incremental QALYs MIGS Vs. Comparator	ICUR of Filtration Surgery Vs. MIGS ($/QALY)
Reference (Trabectome)	**–703**	**–0.070**	**10,093**
iStent Inject [25]	385	–0.214	MIGS dominated (more expensive, similarly effective)
XEN45[65]	–1,053	–0.0003	3,050,721

ICUR = incremental cost-utility ratio; MIGS = minimally invasive glaucoma surgery; QALYs = quality-adjusted life-years; vs. = versus.

[a] Parameters changed: MIGS device costs, intraocular pressure reduction, medication reduction, and complications (details are provided in Table 10 and Table 11).

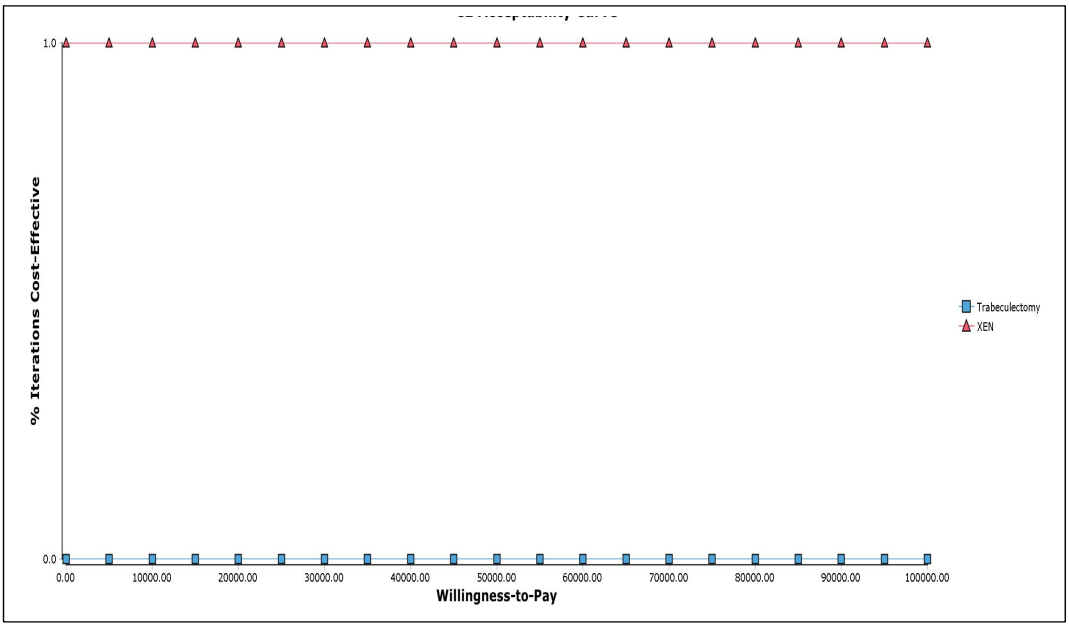
The cost-effectiveness acceptability curves showed that Trabeculectomy was the preferred strategy when compared with iStent Inject (Figure 14). In contrast, XEN45 was the preferred strategy when compared with Trabeculectomy (Figure 15). Of note, the studies reporting the clinical outcomes for alternate MIGS devices that informed the non-reference cases did not provide measures of distribution (e.g., 95% CI, variance). As such, the cost-effectiveness acceptability curves may not truly reflect the level of parameter uncertainty within the analysis as no parameter distribution characterized the clinical efficacy inputs in the model.

Figure 14: Cost-Effectiveness Acceptability Curve for Model 3a (MIGS [iStent Inject] Versus Surgery; Moderate Stage)



MIGS = minimally invasive glaucoma surgery.

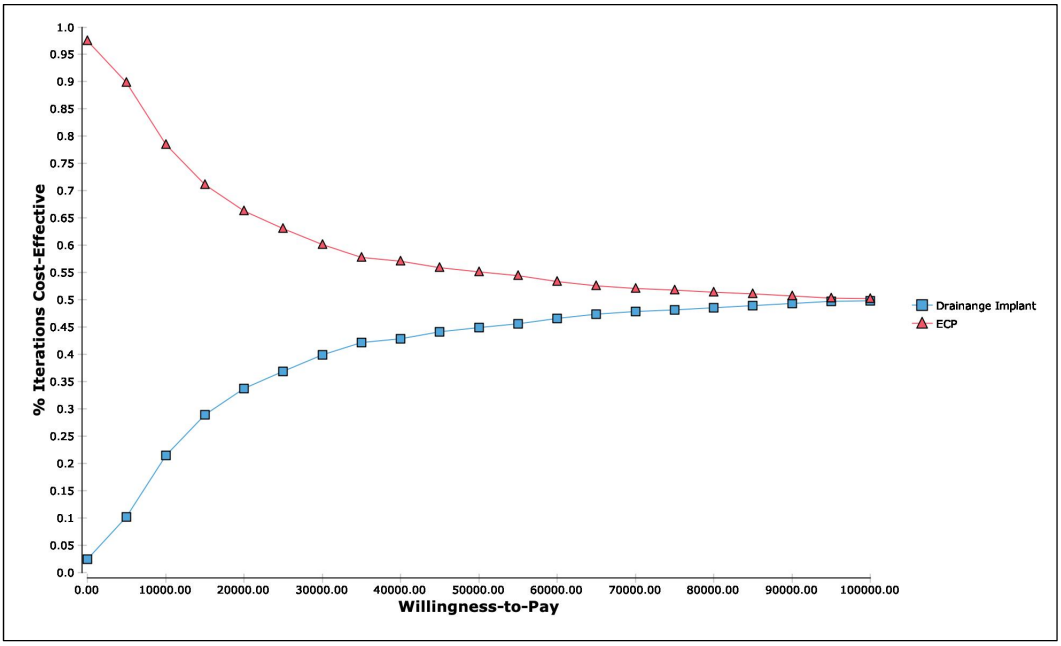
Figure 15: Cost-Effectiveness Acceptability Curve for Model 3a (MIGS [XEN45] Versus Surgery; Moderate Stage)



MIGS = minimally invasive glaucoma surgery; XEN = XEN45.

In patients with advanced-stage disease (Model 3b), there was an incremental cost of $3,267 and an incremental benefit of 0.027 QALYs, leading to an ICUR of $121,959 per QALY gained for filtration surgery versus MIGS (Table 16). The cost-effectiveness acceptability curves were similar to Model 3a; however, the WTP threshold at which filtration surgery would be preferred shifted to $100,000 per QALY (Figure 16).

Figure 16: Cost-Effectiveness Acceptability Curve for Model 3b (MIGS Versus Surgery; Advanced Stage): Reference Case



ECP = endoscopic cyclophotocoagulation; MIGS = minimally invasive glaucoma surgery.

Sensitivity Analyses

For patients with moderate-stage glaucoma (Model 3a), the sensitivity analyses on the reference-case comparison (i.e., Trabectome versus Trabeculectomy with MMC) indicated that filtration surgery remained more expensive than MIGS in all scenarios examined. However, the incremental differences in QALYs did change in some scenarios, leading to fairly dramatic changes in the ICUR from $3.3 million per QALY gained with filtration surgery to filtration surgery being dominant in some cases (Table 21). The instability in the ICUR may be attributed to the very small differences in incremental QALYs observed between treatment strategies.

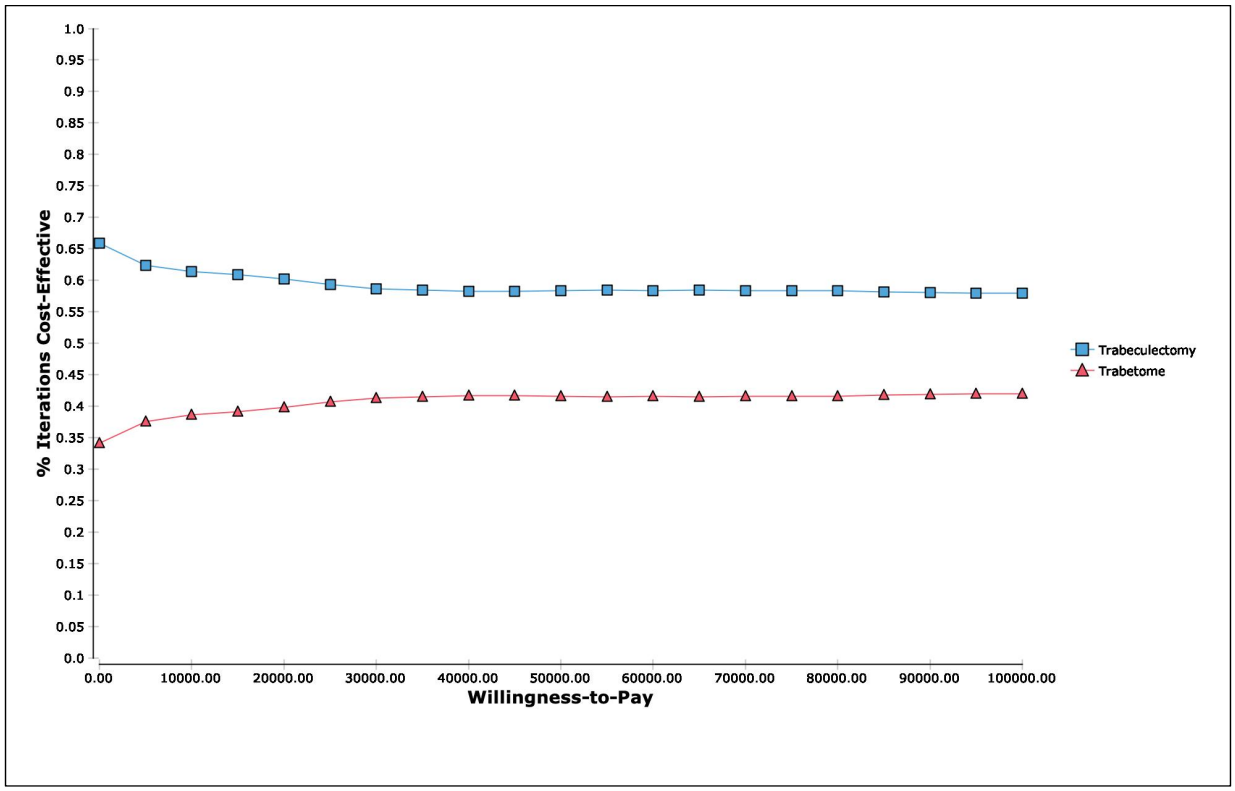
Similar to the reference-case analysis, the sensitivity analyses highlight the fact that the model is highly sensitive to the treatment-related costs. From an Ontario setting (Table 15), whereby the total surgical cost associated with filtration surgery was lower than those costs in Alberta, MIGS was overall more costly than filtration surgery. In such cases, MIGS was dominated by filtration surgery (Table 21). Trabeculectomy was therefore the preferred strategy across all WTP thresholds (Figure 17).

Table 21: Sensitivity Analysis, Probabilistic (Model 3a: MIGS Versus Filtration Surgery, Moderate Stage)

Category	Incremental Costs ($) MIGS Vs. Comparator	Incremental QALYs MIGS Vs. Comparator	ICUR of Filtration Surgery Vs. MIGS ($/QALY)
Reference case	**–703**	**–0.070**	**10,093**
Sensitivity Analyses			
1. One year	–1,341	–0.0004	3,252,450
2. No effect after 12 months	–1,426	–0.003	473,388
4A. 0% discount rate	–578	–0.085	6,834
4B. 5% discount rate	–860	–0.037	23,464
6. No subsequent treatment with filtration surgery	–757	–0.086	8,762
7. Faster baseline VF progression (–0.92 dB annual progression)	–702	–0.098	7,144
8. Slower disease progression per unit of IOP reduction (from Canadian Glaucoma Study)	–760	–0.053	14,348
5. Ontario Setting			
ON cost inputs (combined billing)	417	–0.048	MIGS dominated (more expensive, similarly effective)
ON cost inputs (less intensive billing)	272	–0.062	MIGS dominated (more expensive, similarly effective)
ON cost inputs (more intensive billing)	604	–0.048	MIGS dominated (more expensive, similarly effective)
ON cost and proposed $400 physician fees for MIGS	117	–0.051	MIGS dominated (more expensive, similarly effective)

dB = decibels; ICUR = incremental cost-utility ratio; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; ON = Ontario; QALYs = quality-adjusted life-years; VF = visual field; vs. = versus.

Figure 17: Cost-Effectiveness Acceptability Curve for Model 3a (MIGS Versus Surgery; Moderate Stage): Ontario Setting Assuming Combined Billing



MIGS = minimally invasive glaucoma surgery.

For patients with late-stage glaucoma (Model 3b), sensitivity analyses where the incremental effectiveness was reduced — such as using a one-year time horizon or assuming no difference in effectiveness after 12 months — resulted in smaller incremental QALYs estimated and, thereby, the ICUR increased dramatically (Table 22).

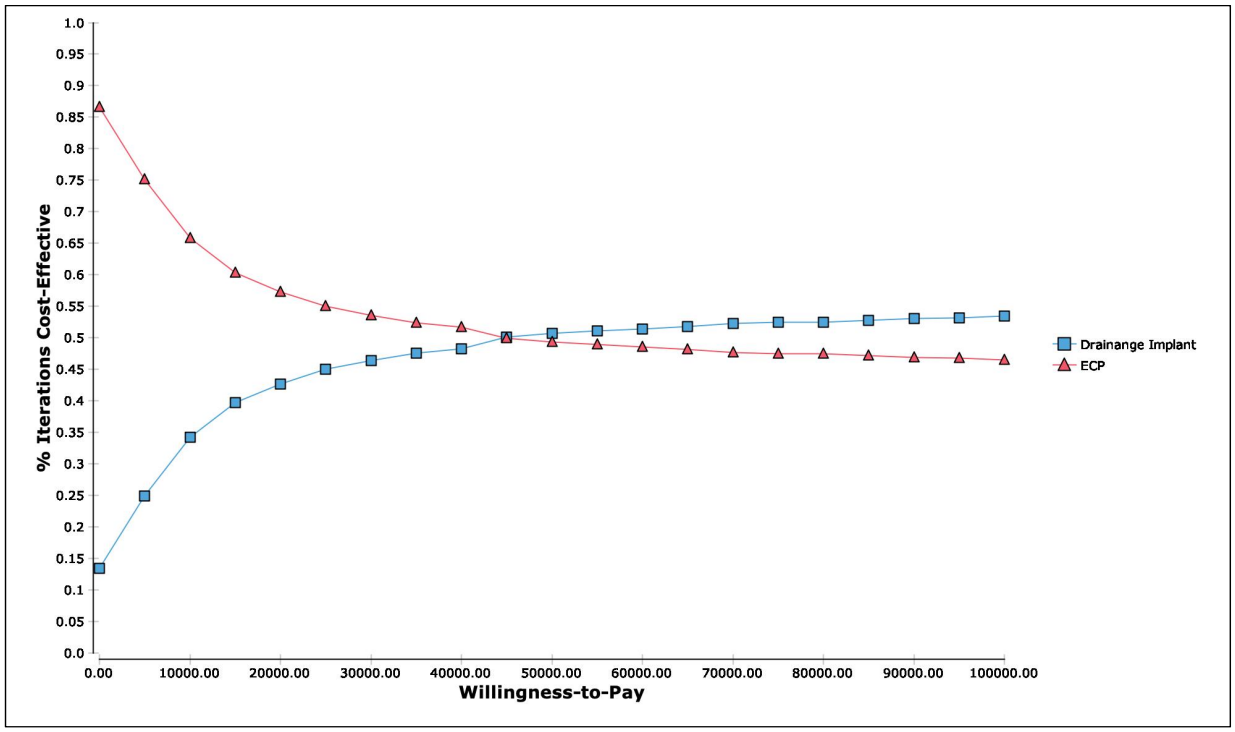
Similar to Model 3a, MIGS became more costly than filtration surgery when Ontario costs were used, as the costs of filtration surgery in Ontario were lower than those in Alberta (Table 10). This resulted in MIGS being dominated (more expensive and less effective compared with filtration surgery) (Table 22).

Table 22: Sensitivity Analysis, Probabilistic (Model 3b: MIGS Versus Filtration Surgery, Advanced Stage)

Category	Incremental Cost ($) MIGS Vs. Comparator	Incremental QALYs MIGS Vs. Comparator	ICUR of Filtration surgery Vs. MIGS ($/QALY)
Reference case	**–3,267**	**–0.027**	**121,959**
Sensitivity Analyses			
1. One year	–3,314	–0.0002	21,485,058
2. No effect after 12 months	–3,315	–0.002	1,365,524
3A. Assumed same IOP between strategies (lifetime)	–3,323	0.00006	MIGS dominant (less expensive, similarly effective)
3B. Assumed same IOP between strategies (one-year horizon)	–3,329	0.00006	MIGS dominant (less expensive, similarly effective)
4A. 0% discount rate	–3,068	–0.036	85,991
4B. 5% discount rate	–3,205	–0.025	126,967
7. Faster baseline VF progression (–0.92 dB annual progression)	–3,168	–0.041	76,821
8. Slower disease progression per unit of IOP reduction (from Canadian Glaucoma Study)	–3,179	–0.044	72,714
5. Ontario Setting			
ON costs inputs (combined billing)	–2,016	–0.041	48,738
ON cost inputs (less intensive billing)	–2,078	–0.041	50,713
ON cost inputs (more intensive billing)	–1,773	–0.044	40,374
ON cost and proposed $400 physician fees for MIGS	–2,160	–0.043	50,705

dB = decibels; ICUR = incremental cost-utility ratio; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; ON = Ontario; QALYs = quality-adjusted life-years; VF = visual field; vs. = versus.

Figure 18: Model 3b (MIGS Versus Surgery; Advanced Stage): Ontario Setting Assuming Combined Billing



ECP = endoscopic cyclophotocoagulation; MIGS = minimally invasive glaucoma surgery.

Interpretation

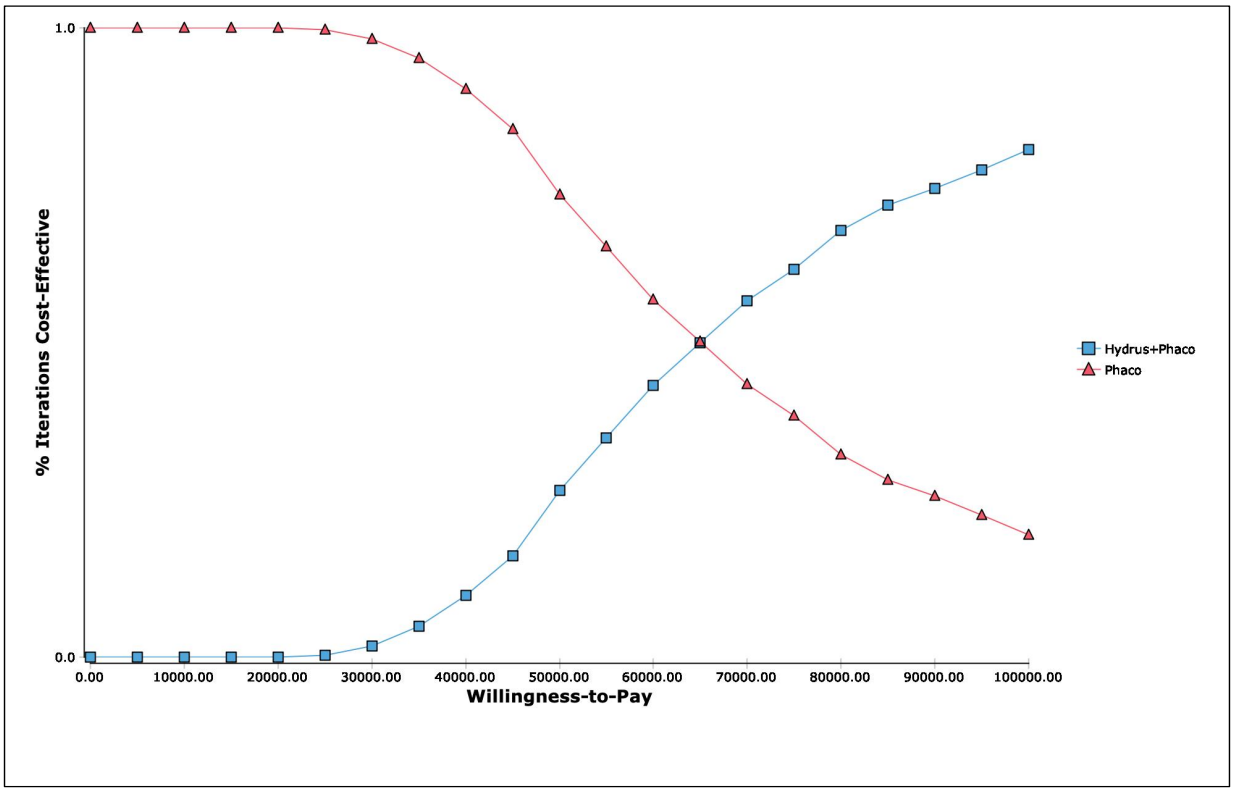
This comparison is different than others seen so far. MIGS was less costly but also less effective than the comparator treatment of filtration surgery, which placed MIGS in a different quadrant of the cost-effectiveness plane. As such, the economic results were interpreted differently as the ICUR was calculated for filtration surgery. As with other comparisons, relative efficacy should be considered with caution. Four of the five clinical studies from the Clinical Review (that considered the short-term surrogate outcome of IOP) were not statistically significant or were not compared statistically. This does not establish noninferiority and, from the probabilistic analyses, MIGS generally was found to be less effective than filtration surgery. In addition, both set of models were highly sensitive to treatment-related costs. As such, future studies are required to provide higher quality clinical evidence on MIGS compared with filtration surgery and detailed costing studies are needed to better inform the Economic Evaluation.

Model 4: MIGS + Cataract Surgery Versus Cataract Surgery Alone

Reference Case and Cost-effectiveness Acceptability Curve

As noted, the reference case was based on a meta-analysis conducted as part of the Clinical Review on the Hydrus Microstent device (Appendix 14). In the reference case, MIGS with cataract surgery was more expensive than cataract surgery alone, resulting in incremental costs of $1,641 over a lifetime time horizon (Table 16). MIGS with cataract surgery was also associated with 0.026 additional QALYs, producing an ICUR of $63,626 per QALY gained. The cost category accounting for the greatest difference in costs between strategies was intervention costs (Table 17), which were estimated to be $3,219 and $1,499 for MIGS + cataract and cataract alone, respectively. The cost-effectiveness acceptability curve (Figure 19) indicated that MIGS + cataract surgery became the preferred strategy above a WTP threshold greater than $65,000 per QALY gained.

Figure 19: Cost-Effectiveness Acceptability Curve for Model 4 (MIGS + Cataract Surgery Versus Cataract Surgery): Reference Case



Hydrus = Hydrus Microstent; MIGS = minimally invasive glaucoma surgery; Phaco = phacoemulsification.

Exploratory Analysis

As other clinical studies on other MIGS devices exist for this pairwise comparison, analyses were conducted on alternative devices to inform the plausible range in cost-effectiveness for MIGS. MIGS with cataract surgery remained more effective than cataract surgery alone. However, caution is required for the clinical effectiveness estimates for ECP and CyPass Micro-Stent as these were from single studies. The estimated QALY difference was larger when clinical efficacy came from single studies than when the clinical efficacy was based on a meta-analysis of multiple studies (i.e., Hydrus Microstent and iStent). Furthermore, as the incremental costs were higher for MIGS with cataract surgery compared with cataract surgery alone, this resulted in a range of ICURs for MIGS from $5,984 to $108,934 per QALY gained (Table 23). The cost-effectiveness acceptability curves highlight the variability in the cost-effectiveness findings between different MIGS devices across a range of WTP thresholds (Figure 20 and Figure 21).

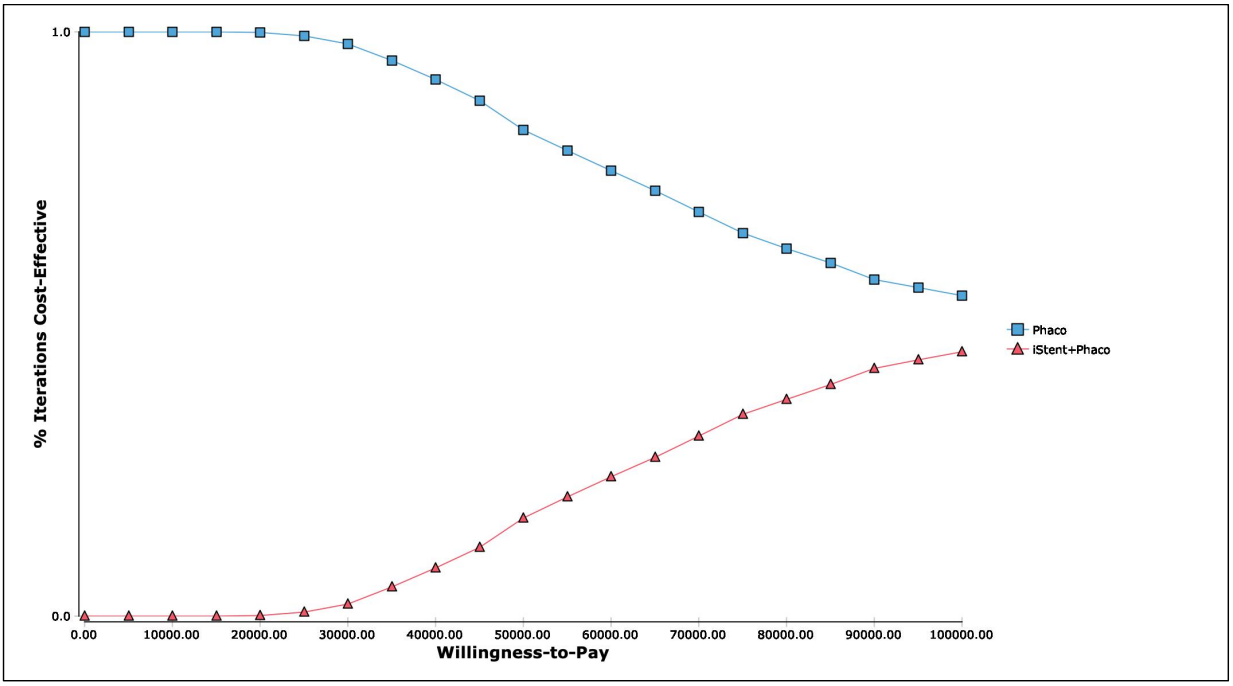
Table 23: Range of Cost-Effectiveness of MIGS With Cataract Surgery Versus Cataract Surgery Alone, by Different MIGS Devices[a]

Category	Incremental Cost ($) MIGS Vs. Comparator	Incremental QALYs MIGS Vs. Comparator	ICUR of MIGS With Cataract Surgery Vs. Cataract Surgery Alone($/QALY)
Reference (MA based on Hydrus Microstent)	**1,641**	**0.026**	**63,626**
iStent (meta-analysis from Clinical Review)	1,754	0.016	108,934
ECP[73]	539	0.090	5,984
CyPass Micro-Stent[70]	1,513	0.057	26,407

ECP = endoscopic cyclophotocoagulation; ICUR = incremental cost-utility ratio; MA = meta-analysis; MIGS = minimally invasive glaucoma surgery; QALYs = quality-adjusted life-years; vs. = versus.

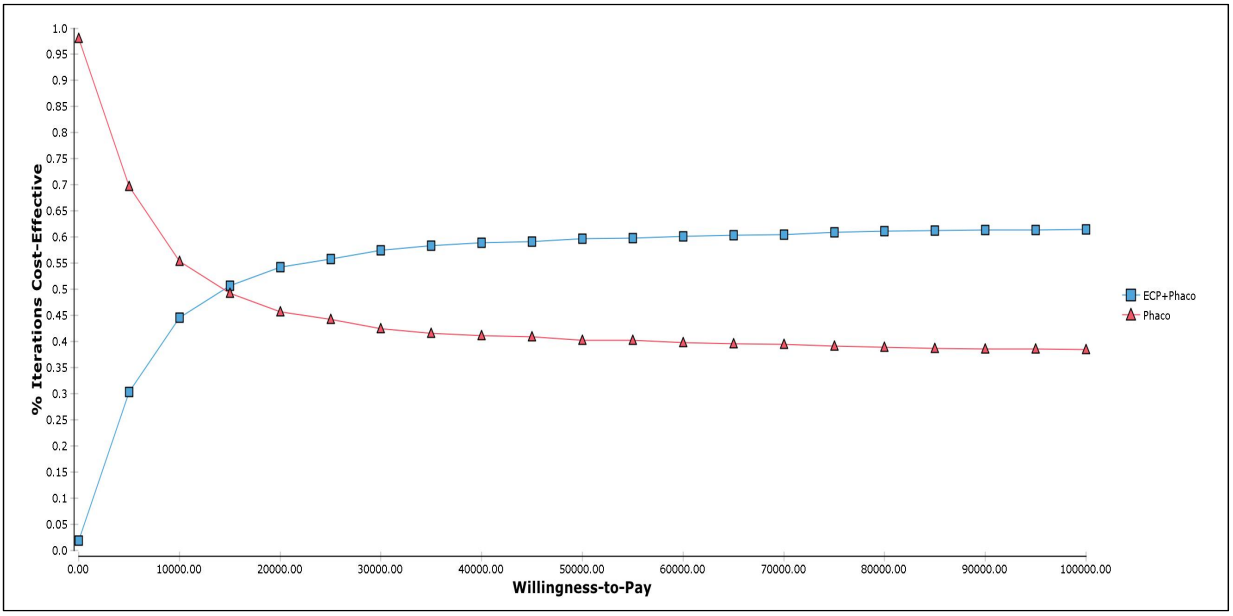
[a] Parameters changed: MIGS device costs, intraocular pressure reduction, medication reduction, and complications (details are provided in Table 10 and Table 11).

Figure 20: Cost-Effectiveness Acceptability Curve for Model 4 (MIGS [iStent Inject] + Cataract Surgery Versus Cataract Surgery)



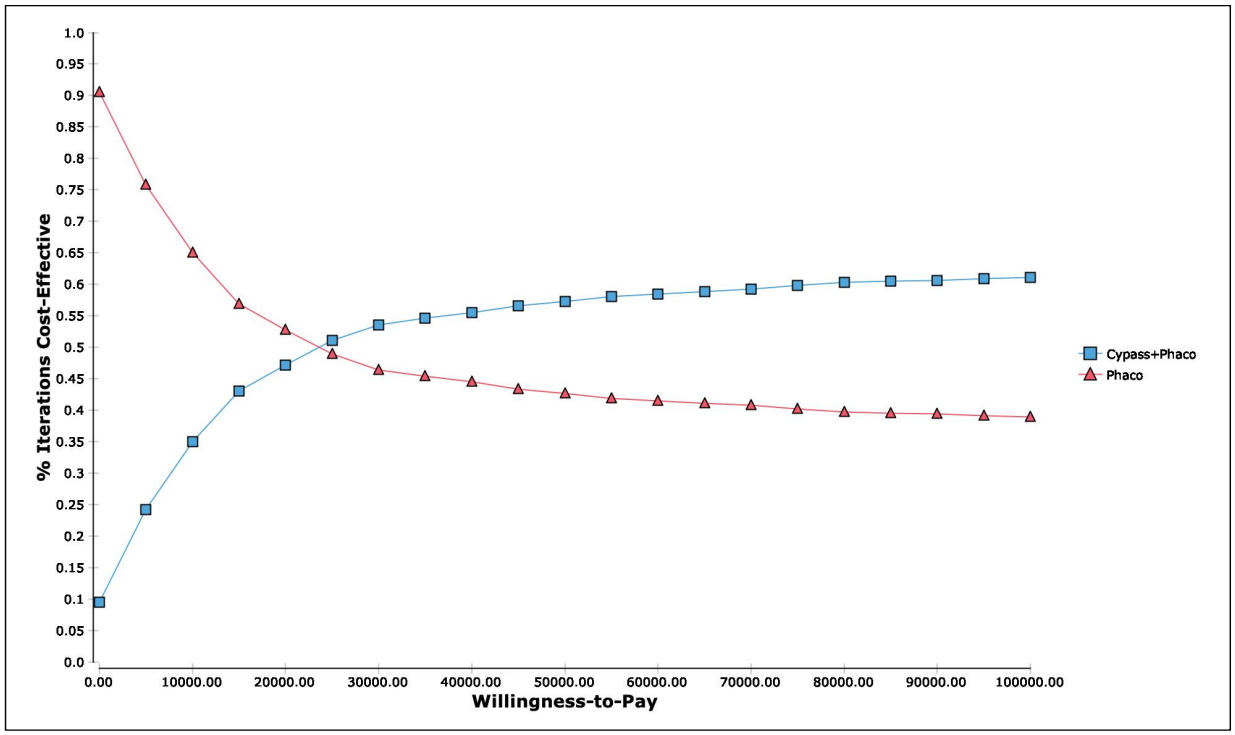
MIGS = minimally invasive glaucoma surgery; Phaco = phacoemulsification.

Figure 21: Cost-Effectiveness Acceptability Curve for Model 4 (MIGS [ECP] + Cataract Surgery Versus Cataract Surgery)



ECP = endoscopic cyclophotocoagulation; MIGS = minimally invasive glaucoma surgery; Phaco = phacoemulsification.

Figure 22: Cost-Effectiveness Acceptability Curve for Model 4 (MIGS [CyPass Micro-Stent] + Cataract Surgery Versus Cataract Surgery)



MIGS = minimally invasive glaucoma surgery; Phaco = phacoemulsification.

Sensitivity Analyses

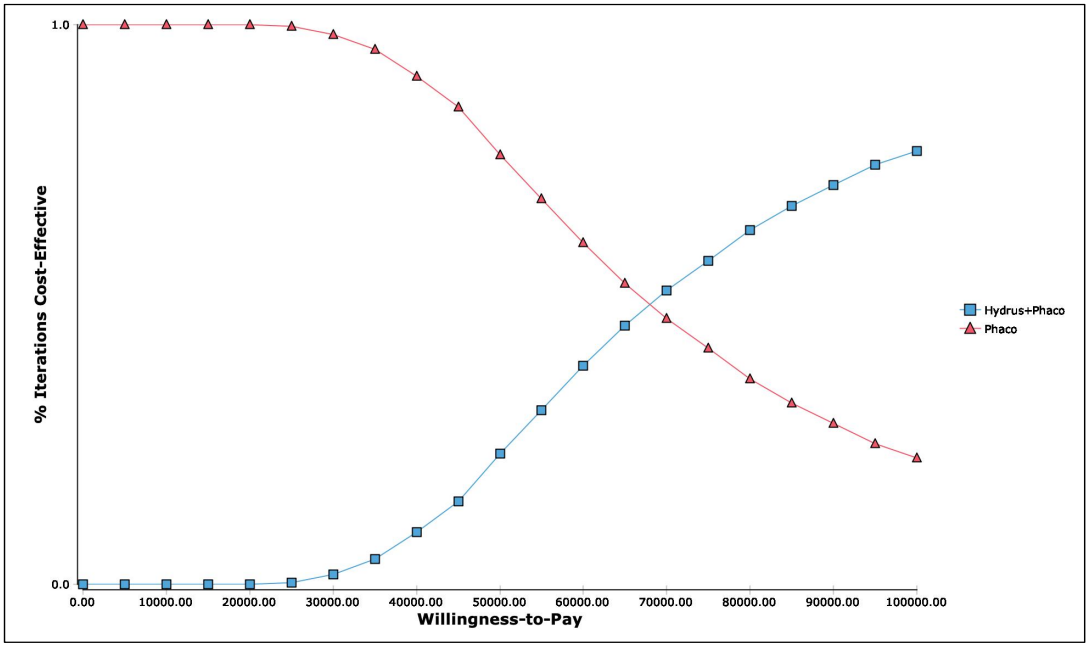
For the majority of the sensitivity analyses, the model's overall findings remained robust (Table 24). Similar to the other models, the model was most sensitive to changes that impacted the clinical effectiveness estimates. In sensitivity analyses where there was no difference in effectiveness between the two strategies after 12 months or where either a one-year time frame was considered, the ICURs ranged between approximately $377,804 and $3,384,115 per QALY gained. The analyses from an Ontario setting were found to be similar to the reference case, regardless of the approach to billing (Table 24); the cost-effectiveness acceptability curve (Figure 23) indicated that MIGS + cataract surgery would be the preferred strategy above a WTP threshold greater than $70,000 per QALY gained.

Table 24: Sensitivity Analyses, Probabilistic (Model 4: MIGS + Cataract Surgery Versus Cataract Surgery Alone)

Category	Incremental Cost ($) MIGS + Cataract Surgery Vs. Comparator	Incremental QALYs MIGS + Cataract Surgery Vs. Comparator	ICUR of MIGS + Cataract Surgery Vs. Cataract Surgery Alone ($/QALY)
Reference case (Hydrus Microstent)	**1,641**	**0.026**	**63,626**
Sensitivity Analyses			
1. One year	1,908	0.0006	3,384,115
2. No effect after 12 months	1,905	0.005	377,804
4A. 0% discount rate	1,632	0.030	54,925
4B. 5% discount rate	1,692	0.019	87,021
6. No subsequent treatment with filtration surgery	1,697	0.030	57,245
7. Faster baseline VF progression (–0.92 dB annual progression)	1,666	0.030	55,741
8. Slower disease progression per unit of IOP reduction (from Canadian Glaucoma Study)	1,646	0.026	63,328
5. Ontario Setting			
ON costs inputs (combined billing)	1,687	0.026	65,873
ON cost inputs (less intensive billing)	1,544	0.026	60,259
ON cost inputs (more intensive billing)	1,824	0.026	69,953

dB = decibels; ICUR = incremental cost-utility ratio; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; ON = Ontario; QALYs = quality-adjusted life-years; VF = visual field; vs. = versus.

Figure 23: Cost-Effectiveness Acceptability Curve for Model 4 (MIGS + Cataract Surgery Versus Cataract Surgery): Ontario Setting Assuming Combined Billings



Hydrus = Hydrus Microstent; MIGS = minimally invasive glaucoma surgery; Phaco = phacoemulsification.

Interpretation

In this analysis, it is clear that treatment-related costs should be greater as an additional procedure (MIGS) is being performed in addition to cataract surgery. There was more clinical evidence available to inform this analysis and, despite its limitations that are common across the other models (e.g., short-term studies using a surrogate outcome); the model was found to be robust to the majority of the sensitivity analyses. The ICUR of MIGS, as a class, added to cataract surgery compared with cataract surgery alone fell within a range between $5,984 and $108,934 per QALY. A limitation with this analysis, that is common across all models, is that it only considered two comparators. Clinical interpretation of these findings must therefore consider the place in therapy between these two comparators along the trajectory of the disease (for example, should filtration surgery with cataract surgery be the most relevant comparator, the findings from Model 5 would be more relevant).

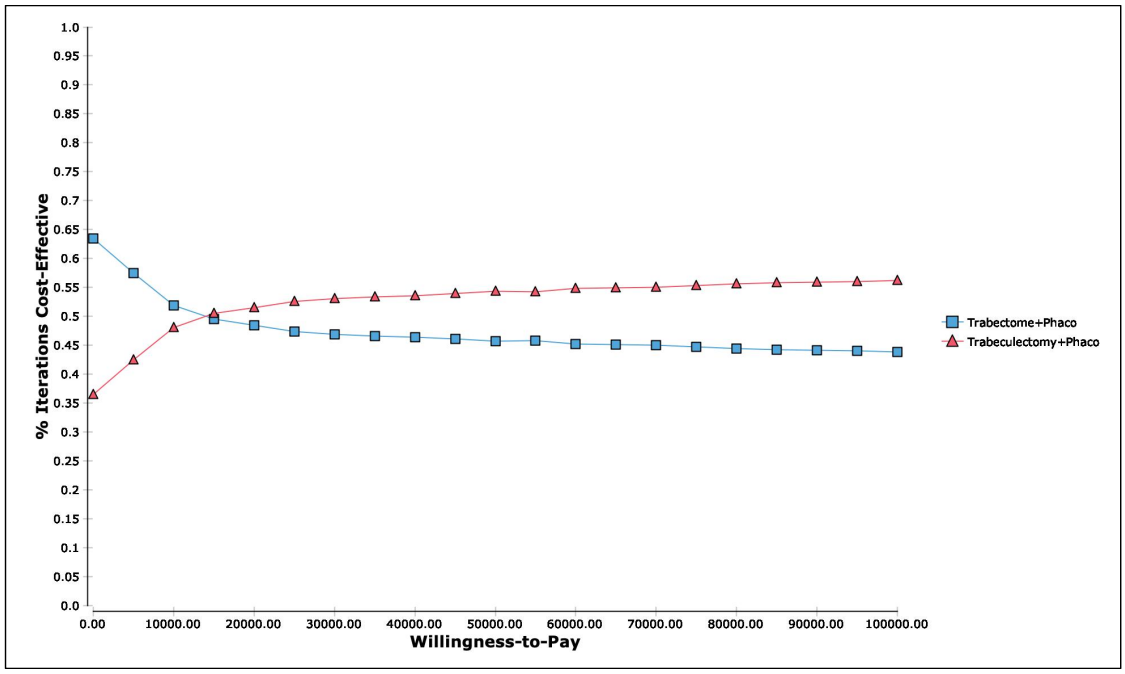
Model 5: MIGS + Cataract Surgery Versus Filtration Surgery + Cataract Surgery

Reference Case and Cost-effectiveness Acceptability Curve

Filtration surgery with cataract surgery was more expensive, but also more effective than MIGS with cataract surgery (Table 16). With incremental costs of $473 and incremental benefits of 0.032 QALYs, this led to an ICUR of $14,968 per QALY gained for filtration surgery + cataract surgery compared with MIGS + cataract surgery. Similar to other comparisons, health state costs formed the largest proportion by cost category although incremental differences within this cost category were small (Table 17) with the major cost driver between strategies being related to intervention costs.

The cost-effectiveness acceptability curve indicated that filtration surgery with cataract surgery was the preferred therapy except when the WTP threshold was approximately below $15,000 per QALY. Above this WTP value, filtration surgery with cataract surgery was preferred in approximately 55% of the iterations (Figure 24).

Figure 24: Cost-Effectiveness Acceptability Curve for Model 5 (MIGS + Cataract Surgery Versus Surgery + Cataract Surgery): Reference Case



MIGS = minimally invasive glaucoma surgery; Phaco = phacoemulsification.

Sensitivity Analyses

Filtration surgery + cataract surgery was more expensive than MIGS with cataract surgery in most scenarios. As there was no statistically significant difference in IOP reduction reported in the clinical studies, if no difference in IOP reduction was assumed, the incremental QALYs became very small between the two comparators. The differences in costs as well as effectiveness observed in sensitivity analysis led to quite varied results with a wide range of ICURs for filtration surgery with cataract surgery.

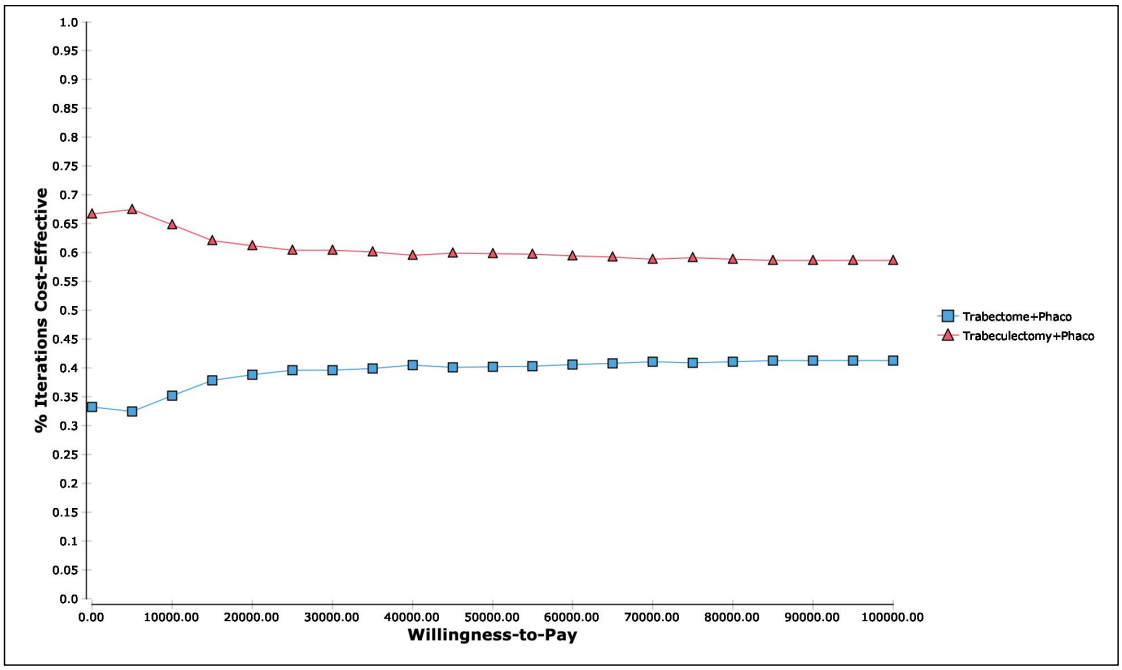
When Ontario costs for both surgeries were used, filtration surgery with cataract surgery was less costly as surgical costs were lower in Ontario compared with Alberta. As such, across all WTP thresholds, filtration surgery with cataract surgery was the preferred strategy in the Ontario setting (Figure 25).

Table 25: Sensitivity Analyses, Probabilistic (Model 5: MIGS + Cataract Surgery Versus Filtration Surgery + Cataract Surgery)

Category	Incremental Cost ($) MIGS + Cataract Surgery Vs. Comparator	Incremental QALYs MIGS + Cataract Surgery Vs. Comparator	ICUR Filtration Surgery and Cataract Vs. MIGS and Cataract Surgery ($/QALY)
Reference case	**–473**	**–0.032**	**14,968**
Sensitivity Analyses			
1. One year	–883	–0.0005	1,838,603
2. No effect after 12 months	–877	–0.008	110,692
3A. Assumed same IOP between strategies (lifetime)	–940	0.0002	MIGS dominant (less expensive, similarly effective)
3B. Assumed same IOP between strategies (one-year horizon)	–946	0.0002	MIGS dominant (less expensive, similarly effective)
4A. 0% discount rate	–396	–0.057	6,914
4B. 5% discount rate	–569	–0.024	23,546
7. Faster baseline VF progression (–0.92 dB annual progression)	–469	–0.042	11,157
8. Slower disease progression per unit of IOP reduction (from Canadian Glaucoma Study)	–471	–0.048	9,879
5. Ontario Perspective			
ON costs inputs (combined billing)	585	–0.037	MIGS dominated (more expensive, similarly effective)
ON cost inputs (less intensive billing)	446	–0.047	MIGS dominated (more expensive, similarly effective)
ON cost inputs (more intensive billing)	690	–0.053	MIGS dominated (more expensive, similarly effective)

dB = decibels; ICUR = incremental cost-utility ratio; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; ON = Ontario; QALYs = quality-adjusted life-years; VF = visual field; vs. = versus.

Figure 25: Cost-Effectiveness Acceptability Curve for Model 5 (MIGS + Cataract Surgery Versus Surgery + Cataract Surgery): Ontario Setting



MIGS = minimally invasive glaucoma surgery; Phaco = phacoemulsification.

Interpretation

As with Model 3, MIGS (with cataract surgery) was less costly but also less effective than filtration surgery with cataract surgery, which placed MIGS in a different quadrant on the cost-effectiveness plane. As such, the ICUR was calculated for filtration surgery (standard of care) compared with MIGS.

The sensitivity analyses highlight the significant uncertainty in the clinical effectiveness due to the quality of underlying studies (see Clinical Review). While in general, MIGS with cataract surgery was found to be a less costly strategy, further evidence demonstrating equivalent or superior clinical outcomes are needed to better ascertain the likely cost-effectiveness of MIGS with cataract surgery compared with filtration surgery with cataract surgery.

4.3 Summary of Results

While the Clinical Review identified many clinical studies that compared the efficacy and safety among MIGS and comparators, there was a lack of high-quality data, and studies were highly heterogeneous, and as such the evidence was not definitive. Pairwise comparisons were used in the reference case as network meta-analysis was not available for any models, and there was high heterogeneity in MIGS devices and patient populations. Specific criteria were used to select the reference case, with sensitivity analysis conducted on the potential range of cost-effectiveness.

Among all models, the incremental difference in QALYs was relatively small over a lifetime time horizon. In the reference-case models, the difference in QALYs among comparators equated to between eight and 25 additional days of perfect health. This can lead to instability of the ICUR if the denominator becomes quite small, as it did in many sensitivity analyses; for example, when equal clinical efficacy was assumed for comparisons that were not statistically significant or in which statistical comparisons were not conducted.

It is notable that the underlying clinical data and evidence that informed difference in effectiveness (and subsequent QALYs) were generally of poor quality, as noted in the Clinical Review. Many of the studies did not demonstrate statistically significant differences in the surrogate outcome of IOP reduction. Further, there is uncertainty in the precise relationship between changes in IOP and its ultimate impact on VF status and vision-related QoL over time. It is notable that many of the differences in incremental QALYs occur over a long time period — when only a one-year time horizon was used, the incremental QALYs were very small among all models. Most of the clinical studies considered outcomes at one year only, and the long-term relative efficacy of alternative treatment strategies is unknown. As such, estimated differences in QALYs should be interpreted with caution as the incremental QALYs were generated over the extrapolation of a lifetime. Ideally, adequately powered studies using clinically important outcome measures should be conducted.

The incremental differences in costs over a lifetime time horizon were also relatively small. In the reference-case model, the differences ranged between approximately $473 and $3,267 per patient. Unlike QALYs, these incremental costs tended to occur relatively early (with the exception of medication costs), largely due to the initial costs of the operation, procedure, and device that occur within the first year. Costs were largely driven by the intervention costs as well as costs due to patients being in different health states, although the incremental differences for health state costs tended to be low between comparators. Other cost categories, including complications and medical costs in general, were relatively small compared with the intervention costs. The intervention costs for filtration surgeries in Ontario were relatively lower compared with those in Alberta (Table 15); thus leading to differences in cost-effectiveness of MIGS. The differences and range of costs reflect both uncertainty (for example, in the true cost of MIGS, or the physician fee that will be used in jurisdictions where one does not exist) as well as variability in costs that may occur between settings and jurisdictions. As such, the attractiveness of MIGS compared with alternative strategies from a cost perspective may differ depending on the cost of the device, the procedure, as well as the physician's claims. Detailed micro-costing of MIGS procedures may allow greater certainty in the true absolute and incremental costs of MIGS.

In summary, this cost-effectiveness analysis considered MIGS versus alternative therapies in patients with varying stages of glaucoma within the disease trajectory. Definitive conclusions on the attractiveness of MIGS from a cost-effectiveness perspective are precluded given the uncertainty in relative efficacy and cost. However, there are some scenarios where MIGS may be attractive, should emerging evidence be supportive. Complexity remains with respect to determining what patients are candidates for all procedures; for example, there may be subgroups of patients with very aggressive glaucoma who may not be clinically appropriate for all treatments. Key areas that may assist the determination of cost-effectiveness include conduct of detailed micro-costing studies of MIGS and comparator interventions, assessment of the impact of medication adherence on disease progression and relative effectiveness (Model 1), and determination of relative effectiveness using clinically important and relevant outcomes. Finally, this analysis examined pairwise comparisons, but did not examine scenarios where there may be multiple treatment options for a patient; this may require further clarification and inquiry prior to recommendations for the optimal use of therapies in patients with glaucoma.

5. Patients' Perspectives and Experiences Review

Overview

Patients' perspectives and experiences of glaucoma and MIGS were incorporated into this HTA through two activities: a systematic review and thematic synthesis of primary qualitative studies and through patient engagement in the form of interviews with three female patients with glaucoma, two of whom had MIGS.

5.1 Methods

5.1.1 Study Design

A systematic review and thematic synthesis of primary qualitative research describing the perspectives and experiences of patients with glaucoma, and those of their caregivers, was conducted. The results of included studies were synthesized using thematic synthesis,[72] an approach that draws on methods for analysis from grounded theory and meta-ethnography.[126] Thematic synthesis is an interpretive approach that facilitated the development of both descriptive and interpretive findings that address the policy question of this HTA.

The review team was comprised of three researchers, two of whom have experience and training in conducting both primary and secondary qualitative research, and another with experience in patient engagement and in systematic reviews of qualitative research.

Research Questions

This review addressed the following primary research question:

Research Question 6:	What are the perspectives and experiences of patients with glaucoma regarding glaucoma and their treatment, and of their clinical and non-clinical caregivers?

To ensure the relevance of the analysis to the purpose of this HTA, a secondary set of research questions was explored during data extraction and analysis. With the primary research question orienting the data selection, collection, and analysis toward patients' and caregivers' experiences and perceptions, the secondary research questions acted as sensitizing concepts during these stages to focus the review.

A. How do patients and their caregivers experience and perceive their glaucoma and their prognosis?
B. How do patients and their caregivers experience and perceive treatment(s) for their glaucoma?
C. What are the ways in which glaucoma and its treatment affect patients' and caregivers' perceptions of their lives?
D. What do patients value or expect with regards to their treatment for glaucoma?
E. Are there differences in perceptions and experiences relating to glaucoma and its treatment between patients, or between patients and their clinical and non-clinical caregivers?
F. What are health care providers' experiences and perceptions of caring for patients with glaucoma?

5.1.2 Literature Search

The literature search was performed by an information specialist, using a peer-reviewed search strategy. The search strategy is presented in Appendix 2.

Information related to patients' experiences was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates; CINAHL (1981–) via EBSCO; PubMed; and Scopus. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were glaucoma, minimally invasive glaucoma surgery, minimally invasive glaucoma surgical devices, and cataract removal surgery. The complete search strategy, including the specific search terms used, is available in Appendix 2.

Methodological filters were applied to limit retrieval to qualitative studies and studies relevant to patients' perspectives. Surveys and questionnaires were also included. No date or language limits were applied.

The initial search was completed August 31, 2017, with an additional search as part of the iterative process being completed on November 20, 2017, to include the concept of cataract removal surgery, which was not included in the initial search.

Regular alerts were established to update the searches until the publication of the final report. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, systematic review repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

5.1.3 Selection Criteria

Inclusion Criteria

Although the search was not limited by language, eligible studies were primary English-language or French-language qualitative studies and mixed-methods studies with separate reporting of the qualitative component. For the purpose of this review, the term "qualitative studies" was operationalized as those studies which use qualitative data-collection methods (e.g., document analysis, interviews, or participant observation) and qualitative data analysis methods (e.g., constant comparative method, content analysis). Studies that have multiple publications using the same data set were included if they reported on distinct research questions; duplicate publications using the same data with the same findings were excluded. Table 26 describes the eligibility criteria used, built using the Sample, Phenomenon of Interest, Design, Evaluation, Research criteria for framing qualitative evidence synthesis research questions.[63,127]

Table 26: Inclusion Criteria for Patients' Perspectives Review Defined Using SPIDER

Sample	Adults with glaucoma; family and friends of persons with glaucoma; health care providers treating adults with glaucoma
Phenomena of interest	Context in which technology is used (e.g., setting, resource allocation considerations, health and human resources issues); how technology fits in the process of patient care; patients' experiences, expectations, and perceptions of glaucoma and its treatment (including medication and surgeries) and prognosis; caregiver (clinical and non-clinical) experiences and perceptions of glaucoma and its treatment (medication and surgeries) and its prognosis
Design	Descriptive (e.g., content analysis, framework approach) and interpretive (e.g., grounded theory, phenomenology) qualitative designs
Evaluation	Context; social relations; perceptions; attitudes; experiences; feelings; expectations; understandings
Research type	Primary qualitative studies (i.e., studies in which authors use methods for both qualitative data collection and analysis); qualitative component of primary mixed-methods studies

SPIDER = Sample, Phenomenon of Interest, Design, Evaluation, Research.

Exclusion Criteria

- Case reports, editorials, or commentaries
- Non full-text publications (i.e., abstracts)
- Studies involving children or youth populations
- Non-comparable health care system

5.1.4 Literature Screening and Selection

Two reviewers experienced with qualitative syntheses independently and in duplicate assessed titles and abstracts of potentially eligible studies in DistillerSR.[128] Disagreements about eligibility at the title and abstract level were resolved through discussion until consensus was reached. The same two reviewers conducted full-text screening of all potentially eligible studies, independently and in duplicate for inclusion. Again, differing judgments about study inclusion were resolved through discussion until consensus was reached.

5.1.5 Data Extraction and Quality Appraisal

One reviewer extracted data describing study and sample characteristics for each eligible study using electronic data extraction forms with a second reviewer verifying descriptive data extraction for consistency and errors.

In addition, two reviewers conducted an independent quality appraisal of the included primary studies. While the ten items from the Critical Appraisals Skills Programme Qualitative Tool[129] were used as prompts for reflection, the appraisal was guided by three primary questions intended to query whether and how a study demonstrated that it collected rich data and conducted a rigorous analysis incorporating reflexive practices leading to robust results that were useful for the objectives of this review: Is it credible? Is it trustworthy? Are the results transferable?[94,130] This approach was piloted using a set of three studies to ensure consistency and coherence between researchers, before continuing independently.

In keeping with the interpretive nature of this review, consensus was not sought between reviewers on the quality appraisal points, acknowledging that there is no "right" answer to

evaluating the rigour and relevance of a study. Rather, differences in judgment were used to probe the methodological and conceptual limitations of the included studies, individually and as a set. These limitations were kept in mind while conducting the analysis. Overall, the appraisal contributed to both the descriptive and interpretive analyses by identifying the limits of transferability of the results of studies within this review.

5.1.6 Data Analysis Methods

A thematic synthesis was conducted, which draws heavily from grounded theory and meta-ethnography.[127,131] From grounded theory, thematic synthesis borrows the constant comparison method, which was practised by comparing concepts (relating to perspectives and experiences) across reviewers, concepts across concepts, and concepts across studies.[131] Further, thematic synthesis borrows the concept of "reciprocal translation" from meta-ethnography, which involves exploring the similarities and dissonances of concepts across studies.[126,132]

Preliminary analysis began at screening through the use of memos, diagramming, and conversation among reviewers. Though still unrefined, this first stage of memoing recorded the primary reviewer's key findings, methodological considerations, as well as descriptive and analytic observations. These memos were then reviewed and discussed as a team to identify a core set of initial concepts relating to the primary research question and sensitizing subquestions. At the same time, an initial patient interview was conducted and used as a way of further orienting the research toward topics and features particular to patients' experiences with glaucoma. Both activities contributed to the development of a pool of included studies with which to begin more active analysis.

While initially intending to pursue formal coding throughout later stages of analysis, given the small number (N = 15) and relative low quality of the included studies, memoing and diagraming continued to be used in lieu of formal coding.[131] The analytic steps of the synthesis remained the same: with open memoing to inductively describe the findings of the primary studies, including their topics, concepts, and dimensions, and their supporting raw data. As such, a second round of memoing and diagraming used an initial, tentative set of concepts to tease out findings and supporting data in the studies and explore their relationships across studies.

Included studies and memos were re-read and key findings and concepts were identified and the linkages between studies were explored. Diagraming was used to explore how emerging concepts mapped onto patients' journey through care, as elicited through primary studies and a patient interview, and how different facets of similar concepts linked together. Using these techniques, concepts were re-ordered and organized into thematic categories. An additional set of patient interviews was conducted and used to further explore types and dimensions of patients' experiences, including those already identified, as well as newly arising ones. Memoing, diagramming, and discussion continued until themes were well-described and stable, and all relevant findings and supporting data from the included studies had been accounted for within those themes.

A final round of memoing used preliminary themes to rework memos, going back to included studies to explore alternative interpretations and divergent cases. The use of diagraming and frequent discussion between reviewers helped to organize and interpret findings, build themes, and articulate and specify their relationships.

5.2 Results

The details of citation screening and study selection are presented in Appendix 17. A total of 7,133 citations were retrieved from the literature search (with duplicates removed). After title and abstract screening, 67 articles were retrieved for full-text review. Of these 67 articles, a further 52 were excluded for the following reasons: participants not majority patients with glaucoma or their caregivers (n = 24), non-comparable health care system (n = 15), duplicate publication (n = 4), primary focus development of a tool or intervention (n = 4), not qualitative (n = 2), non–English- or French-language (n = 2), and not full text (n = 1). Fifteen studies met the inclusion criteria and were included in this review.

5.2.1 Summary of Study Characteristics

The characteristics of included studies are described in Appendix 18. Of the 15 included studies, eight studies were conducted in the UK,[133-141] four in the US,[142-145] one in France and the UK,[146] and one each in Finland[147] and Brazil.[148] Studies were published from 1983 to 2016, with a median publication year of 2010.

As self-reported by study authors, the methods of data analysis used across included studies were content analysis (n = 4),[144,145,147,148] framework analysis (n = 3),[133,139,140] the constant comparison method (n = 1),[134] phenomenology (n = 1)[143], narrative analysis (n = 1),[135] interpretive phenomenological analysis (n = 1),[146] thematic analysis (n = 1),[136] directed content analysis (n = 1),[138] and framework approach (n = 1).[141] One study did not report the method of data analysis.[142] Six studies used interviews as a method of data collection,[135,138,140,146,147,149] five used focus groups,[136,139,144,145,148] and four used a combination of focus groups and interviews.[133,134,141,142] One study reported a qualitative approach that guided the study design (phenomenology), but did not further elaborate on the method of data collection.[143]

5.2.2 Summary of Participant Characteristics

The characteristics of included participants are described in Appendix 19. There were a total of 365 participants within the included studies: specifically, 329 participants with glaucoma (or suspected), five clinicians, and 31 family members of patients with glaucoma. Participants ranged in age from 25 to 93 years, and three studies did not report the age of participants.[135,143,145] The proportion of males in the study samples varied widely, ranging from 21%[136] to 68%.[141]

A variety of measures was used to describe patients' glaucoma, oftentimes using multiple characteristics, including a diagnosis of glaucoma,[133,134,140,143,146-148] use of glaucoma medications and experience of care for glaucoma,[133,137,140,142,148] experience with surgery for glaucoma,[135,148] referral to a glaucoma clinic by a general practitioner or ophthalmologist,[141] VF loss,[136,138,140,148] and poor VA.[133,144]

Six studies involved participants with advanced or severe glaucoma.[133-135,138,144,148] One study involved 25 participants who were suspected to have glaucoma, but were not yet diagnosed.[141] The remaining studies did not report glaucoma severity. Across included studies and within included studies, participants had a wide range of time since diagnosis. Eight studies reported the time since participants had been diagnosed, with a range of one month to 29 years.[133,134,137,138,140,143,146,147] One study reported a mean time since diagnosis of 16 years[146] and another with a median of 20 years.[140] Five studies did not report the time

since diagnosis,[135,136,142,144,148] and one study stated that participants had "long periods of time" since their diagnoses.[143]

Three studies reported participants' occupational statuses: two reported that 33% were still employed[133,142] and another that 20% of participants were still working.[146]

5.2.3 Summary of Quality Appraisal

Overall, the included studies were assessed to be of low quality. Results of the quality appraisal, capturing key points from both reviewers, can be found in Appendix 20.

The criterion of credibility asked the basic question of whether the researchers were true to their participants' voices, and could be demonstrated through clear descriptions of data collection methodology, supporting descriptive analyses with raw data and reflexively engaging with the processes leading to these descriptive analyses. One study was viewed as credible by both reviewers,[134] with the remainder being judged as partially credible (n = 7)[133,135,137,138,140,141,143] or not credible (n = 7).[136,142,144-148] One issue that undermined the credibility of included studies was the absence of consistency between data and findings; for example, when data presented lent to an alternative interpretation or were more supportive of another theme or finding. A second key issue that affected credibility was a lack of reflexive examination regarding assumptions around compliance, which tended to confine data collection to superficial questions surrounding barriers or facilitators to compliance. This limited focus could have prevented researchers from pursuing conversations important to their participants. For instance, while a few studies noted comments around the interplay between gender roles and glaucoma,[134,140,144,145] inquiry into participants' experiences in this space was often not pursued.

The criterion of trustworthiness relates to ideas of dependability and confirmability and the assessment explored issues akin to internal validity of study results. The assessment explored whether the analysis attempted to push beyond a description of participant comments, whether there was analytical consistency throughout, and whether the authors demonstrated reflexive engagement with assumptions. In terms of dependability and confirmability, the results of two studies were viewed as trustworthy,[134,141] with, again, most being judged as partially trustworthy (n = 8)[133,135,137,138,140,142,143,145] or not trustworthy (n = 4).[136,144,146,148] The primary issues that lent the reviewers to question the trustworthiness of the results of included studies related to underdeveloped and conceptually weak analyses. In these cases, reviewers trusted the raw data embedded within findings, but not the primary researchers' themes or findings themselves. Typically this was because the results were presented as categories that were too broad to be conceptual or theoretical findings or themes but were rather topic areas (e.g., knowledge, experiences) and whose relationship to sub themes and concepts were underdeveloped or not described. Journal word limits can severely constrain the reporting of qualitative studies and thus influence judgments around credibility, trustworthiness, and transferability. In the case of the included studies, it is possible that word limits contributed to limited reporting and to assessments of lower quality. However, as the issues found among the bulk of included studies were consistent with methodologically weak and conceptually underdeveloped analyses, they are unlikely to be the result of word count limits alone.

The final criterion for quality appraisal was transferability, in which case the reviewers queried whether the study was relevant to the current review. The assessment was made by exploring reporting of individual study participants, situations, and analyses. In this case, three studies were judged to be transferable,[134,135,141] ten to be partially

transferable,[133,138,140,142-145,147,150] and one to be not transferable.[137] Issues that affected transferability included lack of reporting of patient characteristics, limited trustworthiness, and aforementioned concerns about dependability and confirmability.

5.2.4 Descriptive Analysis

An Unexpected Diagnosis

A diagnosis of glaucoma was often unexpected.[134,135,138,144] Many patients described being first diagnosed in the context of an eye exam scheduled as part of routine eye care.[134,141] While occasionally patients described a critical incident that prompted them to seek care (sometimes even being advised to do so by someone at their workplace),[134,138] by and large patients did not describe seeking care for symptoms. Rather, patients described not experiencing glaucoma symptoms,[144] or not noticing them because of the ways in which symptoms settled in gradually.[134,144] This gradual settling in can mean that patients adjusted to or accommodated symptoms, by either just "living with" vision changes, or by modifying their activities and routines.[134]

When patients did notice vision changes, they readily offered explanations for them that did not invoke to glaucoma (or other medical conditions). Instead, they described experienced vision changes as a symptom of normal aging,[134,138,141,143,147] consistently expressed as the idea that ones' *"eyes are bound to wear out to a degree when you get older"(*p.10).[141] Through these explanations, patients did not interpret or perceive their vision changes as pathological but rather that they were consistent with normal, aging vision. As such, symptoms were not a prompt to seek health care. Instead, patients coped by restructuring how they engaged with everyday tasks.[134,148] Activities such as leaving objects in the same position each time and improving the lighting in their homes helped patients accommodate changes to their sight.[134,141,148]

Patients' general lack of awareness of glaucoma and its symptoms contributed to the lack of patient-driven care seeking for glaucoma-related vision changes.[134,141,144,147,148] This lack of awareness similarly and consistently contributed to the experiences and perceptions of patients across the diagnostic process. Some, who were referred to specialists to confirm the diagnosis, articulated not knowing the reason for their referral, or knew it was eye pressure but did not equate eye pressure with glaucoma.[141]

Personal awareness of and experience with glaucoma was influenced by knowledge of a family of history of glaucoma. Patients who knew they had a family history of glaucoma paid close attention to changes in vision and sought regular eye pressure testing.[138,146] Others who only discovered they had a family history of glaucoma upon diagnosis expressed wishing otherwise as it would have sensitized them to the possibility of having the condition and changed their health care seeking behaviour.[135,151]

Reactions to a diagnosis of glaucoma differ across people, by age, their severity of glaucoma, and over time. One study which focused on African-Caribbean patients diagnosed with advanced glaucoma found that when participants were diagnosed they expressed remorse at not being diagnosed earlier.[151] Few studies probed how length of time since diagnosis affected patients' experiences and perceptions of having glaucoma, although a familiar pattern of moving through emotions, from denial, to anger, to acceptance was expressed by some patients.[140] However, for others, particularly younger patients who face many years of living with a chronic condition, being diagnosed with a condition that is largely confined to persons of older ages was seen to lead to further anger and

frustration.[133] This observation was also heard from patient interviews, where one interviewee articulated how she reluctantly resigned to having to live the remainder of her life with glaucoma.

Glaucoma as Invisible

Glaucoma as invisible relates to two interconnected ways patients experienced and perceived glaucoma. First, glaucoma was something most patients were not initially not aware of — it is unfamiliar, unknown, and as such was not within their view (invisible). Patients consistently described that before diagnosis, and oftentimes afterward, they were unfamiliar with glaucoma — of what it was as a condition, of how it was treated, and what it meant for their vision.[134,141,144,147,148]

Glaucoma was also invisible to patients as they did not experience glaucoma directly. Rather, they experienced vision changes that are the result of damage to the optic nerve by elevated IOP. Until vision changes were substantial, patients' typically experienced glaucoma as an asymptomatic condition.[134,138,141,144,147,148] This is not to diminish the frustration and loss felt by individuals navigating new challenges faced by common and everyday tasks such as reading, driving, or shopping,[134] but rather to note that the diagnosis of glaucoma often fails to take place until these disruptions have begun to become incorporated into daily life.

In a similar way, glaucoma was also invisible to others. Patients and family members reported that their families and coworkers were not aware that they had glaucoma,[133,142,145,147] and this referred both to an unawareness of glaucoma as a condition and how it was experienced by the person with glaucoma. Glaucoma, as a condition, was invisible to others — others could not see vision loss, they could only observe how a person, or their loved one, with glaucoma moved through life. As a spouse of a patient with glaucoma said, *"I think our children even forget he has glaucoma, it is not a big deal"*(p. 928).[133] In some ways, glaucoma also appeared as mundane to outsiders. Perhaps because it is common among older people, its association with aging seemed to contribute to the perception that is just part of normal aging.[138,143,147] Yet the disruption of treatment in the form of eye drops, and its association with blindness, pointed to the ways in which, to people with glaucoma, glaucoma is not mundane.[133-135,148] One patient interviewed by the research team minimized her glaucoma in the face of her sister having cancer, which to her was viewed as a serious condition, unlike her glaucoma. Yet at the same time, she expressed the struggle and burden of lifelong treatment for her eye conditions, particularly as a younger person.

Glaucoma as Blindness

Glaucoma was consistently equated with blindness.[133,134,141-143,146,148] At face value, this is consistent with the clinical pathology of the condition — left untreated, intraocular eye pressure will damage the optic nerve, leading to vision loss. Yet the qualitative studies pointed to other interconnected meanings of "glaucoma as blindness."[134,143] This association between glaucoma and blindness belies a common perception of eye conditions as being either common or normal minor problems (e.g., needing glasses to correct vision) or as those that cause complete sight loss.[134] Glaucoma, not falling into the category of minor vision issues, was instead conceptualized as blindness,[134] where blindness was assumed to be complete vision loss. As one patient articulated*: "I'd never heard of glaucoma — always thought vision [was an] open/shut affair"* (p. 261).[134]

Interestingly, patients whose glaucoma was not advanced describe their experiences of glaucoma not as blindness or as complete sight loss but as vision changes that affect their day-to-day lives. Loss of vision played out in a myriad of ways — from changing or even limiting how patients engaged in social and economic activities to their activities in the home.[134,140,145] That study participants tended to be older adults meant they were, by and large, no longer employed; many of the activities affected by their glaucoma centred around the home and their social lives.

Patients consistently spoke to the ways in which they desired to preserve what sight they had left, expressing the greatest concern over retaining their ability to drive and to read.[133,134,140,143] Yet for all the multifaceted ways in which vision changes due to glaucoma affected patients' everyday lives, these experiences did not correspond with the conceptualization of glaucoma as blindness and as total vision loss. It is not that patients experience glaucoma as blindness; rather, the findings suggest, it is the spectre of blindness lurking in glaucoma that is deeply troubling to patients.

Across studies, patients articulated a fear of blindness.[133,134,144,148] Authors of included studies tended to not probe this fear, leaving it instead as a normal emotional reaction to living with glaucoma.[133,144,148] This fear was evoked in some patients and motivated their efforts to use their treatment as prescribed.[133] A closer reading across studies, however, drew out that fearing blindness was often connected to a patient's fears of being unable to engage in the world, a sense that the ability to live a life with meaning was dependent upon retaining vision.[143] These descriptions imply that being blind impairs one's independence and mobility, leading to isolation and dependence.[134,140,143] Indeed, participants, even those legally considered blind, tended to describe people who are blind as being either heroes, brave souls who conquer the adversity of being sightless,[134,143] or as victims, those who are isolated and helpless in the world and are to be pitied.[134,143]

As such, it seems patients' views of glaucoma were heavily shaped by pre-existing perceptions of what it means to be blind,[134] and these in turn shaped how patients with glaucoma reacted to and interacted with their glaucoma. People who were legally blind described that they did not want to be identified as blind,[134,140] and others described keeping their glaucoma hidden to avoid being seen as helpless.[140,143] Keeping their glaucoma hidden often meant patients did not seek accommodations for their vision condition; for example, not using a white cane[134,140] or by not asking coworkers to dim the lights in a meeting space.[148]

Gender roles emerged in a variety of ways, with female patients describing feeling guilty at having to involve male partners in domestic chores and caregiving for children,[134] and stating they received support much less often than they would have liked.[144] Gender differences in social roles also played out in the impact of diagnosis, with women expressing worries around their caregiving roles and men with their occupational roles and ability to drive.[140,145] The impact of gender roles appeared to be more pronounced in older patients among whom gender roles may be more fixed and traditional as compared with current trends in the politics of gender.

The Disruption of Eye Drops

Many of the included studies described the challenges patients face with eye drops, their primary treatment for glaucoma.[133,141-143,145,146,148,152] While some patients described that these challenges were only faced when they first began using them, after which they found ways to take the medications as prescribed, challenges lingered for others.[133] Some patients

even raised their previous struggle with eye drops after they stopped having to take them post-surgery.[148] These challenges arise in the face of a medication regime that requires multiple drops at multiple times of the day, which frequently have side effects (both temporary, such as stinging or watering eyes, and long-term, such as in eye lashes growing long or dry eyes).[133,140,142,146,148] While studies tended to describe patients as forgetting to take medications, patients' descriptions of their behaviour was not merely a matter of not remembering. Patients' themselves described being too tired or busy to take their drops,[142] and of struggling to keep track of time and requiring reminders[133,142,145,146,148] highlighting the ways in which attempts to adhere to eye drops can disrupt patients' lives.

"If you've got a daily rhythm of things you do at certain times it's easy. I think it's when you go and do other things that take you away from the general routine, then you might forget it" (p. 928).[133]

For some individuals, these disruptions to daily life were overcome at the expense of much effort and thorough planning and preparation. From medication logs to integrating their eye drops into already established daily routines (e.g., placing medication by their toothbrush so when they brush their teeth, they are reminded to take their medications [133]), many patients described using a host of techniques to take the right drops at the right time.[133,145,146,148]

For others, these types of activities were both impossible and impractical. This impracticality was often tied to the need to take drops during daytime hours, which could bump into difficulties like simply being busy, finding an appropriate location, keeping the drops cool while out of the house, or coping with stinging or watering eyes after taking drops while needing to being active.[133,140,148] Again, with the importance of routine in taking eye drops, changes in routine such as travel[133,146,148] presented as further disruptions that required additional effort to be overcome.

A final set of challenges relate to the specifics of the act of taking eye drops. Patients reported experiencing challenges with grip, balance, and precision when trying to install drops.[133,141,146,148] Advancing age and comorbidities such as Parkinson's, arthritis, and tremors also makes taking drops more difficult for some.[133,145] Some studies noted that while patients knew the steps of how to take eye drops, they did not always do them in the "proper" order.[133,142] When confronted with the idea that they were doing it wrong, they expressed frustration.[142]

Despite these challenges, some described that they persevered their medication regimens based on a fear of their condition worsening or of becoming blind.[140,146] Others articulated a sense of the futility of taking eye drops as they did not result in any noticeable changes in their condition.[133,146] As one patient put it: *"After the years I've just got used to it and I think that isn't gonna make much difference missing just one"* (p. 928).[133]

These experiences with the taking of eye drops relate back to the theme of glaucoma as invisible and to the difficulties in treating a chronic condition that requires lifelong pharmacotherapy of non-detectable, or invisible, symptoms. For instance, when reflecting upon the chronic nature of glaucoma, one patient described: "*[a]t the beginning, it makes me think, a lifelong treatment is never something pleasant."*[146] The younger one is at diagnosis, the more daunting the chronicity of glaucoma and its care can seem. As another patient noted:

"I suppose I feel like I'm standing at the bottom of Everest looking up (isn't it) I mean here I am, at 52, and I suppose I think well, perhaps I'll last until 80 or so, so 30 years of eye drops… it does seem a long while to take eye drops for" (p. 928).[133]

The culmination of invisibility, chronicity, and therapeutic requirements played out across varying lifespans have the ability to place immense psychological strain on individual's living with glaucoma.[140,143] Not surprisingly, patients articulated wishing they had to take drops less often,[142] as well as a desire to explore alternatives such as combination drops and new medications.[142]

Perceptions and Experiences of Eye Surgery

Three studies reported on patients' views and experiences of filtration surgery.[136,148,151] Patients described being fearful and anxious of eye surgery because of how delicate eyes are:[136,151] *"the most delicate part of the human body"* (p. 6).[151] Related, some saw eyes as precious: *"I've never missed an appointment because I think your eyes are the most precious things in your body."*[136] In a visual-centric society, being able to see is of paramount importance and the possibility of AEs, including risk of blindness, led some to be more conservative in assuming the risks of surgery.[136] To some, surgery was thus viewed as a "last resort," only to be conducted once all other treatment options had failed.[136,153] One study reported patients as describing that if they already had visual impairment, they would be more willing to risk surgery.[136]

Patients' views of surgery appear to hinge on the extent to which they trust their surgeons, with patients' agreeing to go ahead with surgery because they "trust the doctor."[136,148,151] Others viewed surgery favourably as it offered the ability to eliminate the need for what they perceived to be ineffective and disruptive eye drops. Despite being free from the routines and rhythm of eye drops post-surgery, some patients remained troubled about their glaucoma and the potential need to use eye drops once again.[148]

While no studies specific to MIGS were found, interviews with patients who had undergone MIGS indicate that these conversations around filtration surgery map onto those regarding MIGS.

Clinical Encounters — the Patient–Provider Relationship at the Centre of Care

Beyond the previously discussed need to trust surgeons, several studies reported patients' perspectives and experiences of the clinical encounters that make up an integral part of a patient's journey through the health care system.[135,141,144-146] Taken together, they give some sense of the character and range of clinical experiences encountered by patients with glaucoma and the centrality of the patient–provider relationship.[135,144-146]

For example, some studies reported the ways in which the patient–provider relationship is key at the point of diagnosis. In one investigation of patients diagnosed with advanced glaucoma, the authors found that even though many of the participants reported going for routine exams, their diagnosis was delayed because it was not detected by providers or there was a breakdown in communicating the need for follow-up care and referral.[151] At times, patients perceived the delay in their diagnosis to their symptoms being ignored by physicians.[138]

Clinical encounters with providers were seen to shape patients' experiences of their condition and treatments. This became particularly apparent in the experience of a chronic condition, like glaucoma, which spans a patient's lifetime.[144] For some, their providers

served as mentors, providing reassurance through their care.[135,146] Other patients described their appreciation of having a provider who would change their medications to address side effects and took time to listen to their concerns,[133] and their discomfort with those who downplayed their condition.[141] At the same time, some patients described not disclosing their side effects to their provider, the reasons for which were not explored.[142]

Further, descriptions of clinical encounters between patients and providers revealed facets and dimensions of the health care systems in which they were situated. Patients often acknowledged the constraints in which providers were operating — what they perceived to be a high pressure and overloaded health care system.[133,141] Some patients felt education about their conditions and treatments had been "unsatisfactory" as the result of providers being too busy due to pressures on the health care system.[133] In some cases, providers were seen as too busy to ask their patients questions, and patients reported not wanting to take up the time of other patients who were waiting.[141]

Additional considerations relate to wait times for specialists. While those who did not know much about glaucoma described themselves as untroubled by a six-month wait to see an ophthalmologist, long wait times to see specialists were reported to raise feeling of anxiety and worry for patients, who waited in anticipation of news of their condition and of changes to their medications.[141] For example:

"When I first knew and I got the appointment, and it was six months away, I was — I suppose I was scared. I thought, 'crikey,' that's going to be another six months that my eyes are deteriorating and no one's going to even look at them."[141]

5.2.5 Analytic Synthesis

The Problems of Compliance and Caring for Oneself

The language of "compliance" was the starting point for many of the included studies, with researchers often exploring (from the perspective of patients with glaucoma) reasons for non-compliance and what stood in the way of (barriers) or helped (facilitators) them become compliant.[133,141-144,147] Alternate language to probe the same concept was sometimes used; for example, "nonadherence to medications." In both cases, the concept of compliance implies that patients ought to do as advised by their physicians to achieve treatment goals. Indeed, one of the included studies defined compliance as *"an active, intentional and responsible process of care, in which the individual works to maintain his or her health in close collaboration with health care providers"* (p. 490).[147]

Understanding patients' behaviours through the lens of compliance focuses the burden of non-compliance onto the patient. In this way, patients who do not comply may be viewed as deviant, and their behaviour as something to be corrected. With the focus on non-compliance, the studies included in this review missed an opportunity to explore the slippage between physicians' treatment goals and patients' experiences of their treatment. As the descriptive findings note, patients do not directly perceive elevated IOP, with patients typically making reference to "the pressure" in the context of the need to take eye drops.[141,148] As a largely asymptomatic condition, glaucoma is experienced by patients as the disruption in their lives by eye drops, as interactions with health care providers, and ideas and worries about blindness. With this in mind, it is not surprising that for patients, treatment goals may focus more on the quality of interactions with health care providers and opportunities to streamline or reduce medication burden, with the overarching goal of being able to retain their sight and current way of life. A focus on compliance engages superficially

at best with patient-important experiences that shape QoL and misses opportunities to take seriously the challenges (medication burden and side effects) of existing pharmacotherapies for glaucoma, as well as the benefits or detriments of an option like MIGS from a patient's perspective.

5.2.6 Canadian Patients' Perspectives and Experiences

Although none of the included qualitative studies were conducted within Canada, stakeholder feedback received in the context of this review provided some indication of the perceptions and experiences of Canadian patients with glaucoma.

The Foundation Fighting Blindness recently conducted an online survey to better understand some of these burdens. Collecting information on the physical, psychological, financial, and other burdens associated with the disease, the survey was made available to Canadian patients with glaucoma between July and September 2018. During that period the survey received 244 responses, providing a range of insights into the experiences of patients across Canada. Data from the survey were reviewed by the Foundation Fighting Blindness in collaboration with the Canadian Council of the Blind and the Canadian National Institute for the Blind, who then submitted collective feedback on CADTH's study of MIGS. Survey respondents were mostly located in Ontario (73%), with the remainder in British Columbia (12%), Alberta (5%), Quebec (3%), Newfoundland (2%), Nova Scotia (2%), Saskatchewan (2%), and Manitoba (1%). The average year of birth provided by patients was 1950 and the average year provided for a glaucoma diagnosis was 2000. (Dr. Chad Andrews, Foundation Fighting Blindness, Toronto, ON; Ms. Louise Gillies, Canadian Council of the Blind, Ottawa, ON; Dr. Mahadeo Sukhai, Canadian National Institute for the Blind, Toronto, ON: personal communication, 2018 Oct 24).

Responses emphasized the profound impact glaucoma can have on the lives of patients, with the largest group indicating that they consider the disease to be "very serious" and that they think about it at least once a day. Respondents also foregrounded a diverse range of challenges associated with the disease, encompassing activities many would consider indispensable, such as driving, as well as the smaller and more personal intricacies of daily life, such as sewing, being physically active, and repairing equipment. While most respondents were aware of the treatments they are currently receiving, the majority indicated that they have not been made aware of any treatments that could function as an alternative. At the same time, the majority selected that they would be willing to try a different treatment or medication if a more effective one was offered, particularly if it was recommended by their specialist or physician. When rating their level of comfort with available treatments, respondents indicated the highest level of comfort with pharmacotherapy, followed by laser surgery, then MIGS, and finally, traditional surgical options. (Dr. Chad Andrews, Foundation Fighting Blindness, Toronto, ON; Ms. Louise Gillies, Canadian Council of the Blind, Ottawa, ON; Dr. Mahadeo Sukhai, Canadian National Institute for the Blind, Toronto, ON: personal communication, 2018 Oct 24).

5.3 Summary of Results

Most times a diagnosis of glaucoma was unexpected, occurring during a routine eye exam. Although a critical incident occasionally prompted patients to seek vision care, by and large patients described themselves as asymptomatic. When patients did notice vision changes, they typically interpreted them as part of normal aging and nothing to seek care for.

The impact of a diagnosis of glaucoma varied depending on the severity of glaucoma at diagnosis, age, and gender, and on how individuals participated in social and economic activities. Gender roles influenced patients' perceptions and experiences of glaucoma, particularly as they shaped social roles and expectations. Women described worries and struggles in caregiving and domestic roles, while men saw vision loss as particularly challenging in the ways it impacted their employment and ability to drive. Patients diagnosed at younger ages face many years of living with glaucoma, and the experience of having a condition typically found among older persons can lead to anger, frustration, and a sense of isolation for some.

Patients consistently described that before diagnosis, and oftentimes afterward, they were unfamiliar with glaucoma — of what it was as a condition, of how it was treated, and what it meant for their vision. Patients equated glaucoma as blindness and feared becoming blind, and wished to preserve their remaining sight, in particular to retain their ability to read and drive. Views of glaucoma were heavily shaped by pre-existing perceptions of what it means to be blind. Patients who were legally blind did not want to be identified as blind and kept their glaucoma hidden, and did not seek accommodations or use vision aids (e.g., a white cane) in order to avoid being seen as helpless or as a tragic figure.

Eye drops — the front line of therapy for glaucoma — were constantly described as disruptive for patients. While some patients described only facing challenges when they first began using eye drops, challenges lingered for others. These challenges emerged through descriptions of a medication regime that requires multiple drops at multiple times of the day, which frequently have side effects, both short and long term. Patients described a host of techniques to help them take the right drops at the right time, yet most still struggled to fit eye drops into an active and busy life.

Not surprisingly, patients wished they could take fewer drops less often and wanted to explore alternatives to their current treatments; for example, combination drops and new medications. Patients' views and experiences of glaucoma filtration surgeries varied widely, with some seeing surgery as a "last resort" only to be undertaken after all other treatment options had failed. For others, surgery was a viewed as a positive option when recommended by a surgeon in whom they trusted, which would offer freedom from the regime of eye drops.

Patient–provider relationships emerged as a central component of patients' experiences of glaucoma and its treatment. Patients reported appreciating providers who would change their medications to address side effects and who listened to their concerns. Yet they acknowledged the constraints under which they observed providers were operating — a high pressure and overloaded health care system in which doctors were seen as too busy to be asked questions. Patients also described the ways in which long wait times to see specialists and get news of their condition and changes in medications can raise feeling of anxiety and worry.

Within the included studies, caring for glaucoma was equated with being compliant with pharmacotherapy, with the goal to decrease IOP. Yet glaucoma was not experienced as elevated IOP by patients, but rather as an asymptomatic condition, accompanied by the fear of (further) vision loss, and the disruption of eye drops. Patients were motivated to care for themselves and take medications to avoid blindness and its potential impact on their lives, but they did not use the language of IOP. Thus, a slippage exists between the clinical goals and language of treatment (i.e., to reduce IOP to retain vision) and patients' goals and language of treatment (i.e., to continue to be able to see in order to live their independent lives).

6. Ethical Issues Analysis

The Ethical Issues Analysis addressed the following research questions:

Research Question 7:	What are the major ethical issues raised by the use of MIGS devices and procedures?
Research Question 8:	What are the broader legal, social, and cultural considerations?

Review of Empirical and Normative Bioethics Literature

The purpose of this analysis was to identify and reflect upon key ethical concerns that should be considered when comparing the relative merits and demerits of MIGS versus pharmaceutical management or filtration surgery for the treatment of glaucoma in adults in Canada. Though other sections of this HTA implicitly touch upon broad ethical concerns, the aim of this analysis is to make such issues explicit and to identify others that may be relevant to any decisions in this regard. The issues raised in this section necessarily go beyond narrowly defined ethical concerns to encompass broader legal, social, and cultural considerations, as well. It is common in the ethics literature, across a broad range of health-related issues, to refer to ethical, legal, and social issues (ELSI) when addressing broader values related considerations. While the primary emphasis here will be on ethical considerations, social factors also figure in the discussion.

6.1 Methods

6.1.1 Literature Search Methods

The literature search was performed by an information specialist, using a peer-reviewed search strategy.

Ethics-related information was identified by searching the following databases: MEDLINE (1946–) via Ovid, PsycINFO (1806–) via Ovid, CINAHL (1981–) via EBSCO, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were glaucoma, minimally invasive glaucoma surgery, and minimally invasive glaucoma surgical devices.

Methodological filters were applied to limit retrieval to studies related to ethical, legal, and social issues. Retrieval will be limited to documents added to the databases since January 1, 2000. The search was limited to English- or French-language publications.

The initial searches were completed by November 2017. Regular alerts were established to update the searches until the publication of the final report. Regular search updates were performed on databases that do not provide alert services.

Studies meeting the selection criteria of the review and identified in the alerts prior to the completion of the stakeholder feedback period were incorporated into the analysis of the final report. Studies that were identified after the stakeholder feedback period were described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

6.1.2 Selection Criteria

Articles, studies, and reports were included if they explicitly and specifically raised ELSI issues related to the central question of this HTA, as well as literature which, though not explicitly about ethical issues (e.g., an empirical investigation of patient attitudes about MIGS versus pharmaceutical management of glaucoma), may point to potential ethical issues even if the participants and researchers did not formulate them as such.

6.1.3 Selection Method

The selection of relevant literature proceeded in two stages. In the first stage, the title and abstracts of citations were screened for relevance by a single reviewer. Articles were chosen to be reviewed in full-text form according to the following criteria:

- provided normative analysis of an ethical issue arising in the use of MIGS or pharmaceutical management of glaucoma
- presented empirical research directly addressing an ethical issue arising in the use of MIGS or pharmaceutical management of glaucoma
- explicitly identified but did not analyze or investigate empirically an ethical issue arising in the use of MIGS or pharmaceutical management of glaucoma.

In the second stage, the full-text reports were reviewed by a single reviewer. Reports meeting the previously mentioned criteria were included in the analysis, and reports that did not meet these criteria were excluded.

Because no published studies were retrieved either in the commercially published or grey literature that directly examined ELSI bearing on glaucoma or MIGS, the selection criteria was broadened to include bodies of research and commentary that dealt with issues indirectly or analogously related to potential ethical issues identified through expert recommendations in an Environmental Scan, titled *Minimally Invasive Glaucoma Surgery: Implementation Considerations,* which was conducted to identify and summarize information regarding the current practice and the implementation of MIGS devices and procedures in Canada.[154] Further details on the Environmental Scan is described in the Implementation Issues Analysis.

The goal in a review of bioethics literature is to canvass what arises as an ethical issue from a broad range of relevant perspectives. As such, the quality of normative analysis does not figure in the article selection criteria: any identification of an issue by the public, patients, health care providers, researchers, or policy-makers is of interest whether presented through rigorous ethical argumentation or not. For example, academic ethicists may focus on certain issues because they relate to theoretical trends in their discipline, while an opinion piece by a clinical or policy leader or a patient may bring to the fore ethical questions that are neglected by academic ethicists but are highly pertinent to the assessment of the technology in the relevant context. Despite the different standards of normative argumentation for each kind of report, the importance of the issues raised cannot be

assessed solely by these standards and so literature cannot be excluded based on methodological standards.

6.2 Results

Assessment of the ethical and social considerations around the optimal use of MIGS in Canada must be grounded both in published literature and in relevant facts about the current usage of MIGS in Canada and elsewhere. Two major findings of fact bear on the ethical and social analysis that follows.

First, there is a disparity between the existing quality of evidence on the clinical effectiveness of MIGS and the belief in its value manifested in the adoption of MIGS by Canadian specialists and hospitals to date. The Clinical Review of this HTA, with the quality of evidence ranging from "very low" to "high" across outcomes, comparisons and study designs, suggests that there is largely insufficient evidence for the comparative clinical effectiveness and safety of MIGS, either alone or in combination with cataract surgery, versus other glaucoma treatment modalities. Bearing in mind that MIGS is not a single technology but a range of heterogeneous surgical procedures and devices, it is also notable that evidence is lacking both for the relative benefits of any given MIGS device or procedure over any of the others, either overall or for a subset of patients.

Despite this limited evidence, professionals who are "early adopters" of MIGS — such as those consulted for the CADTH Environmental Scan[154] — believe strongly in the potential of this technology to offer a valuable new option in the pathway of glaucoma care. The availability of a new treatment modality through surgery (as opposed to medication) is particularly relevant given that a high proportion of earlier-stage patients with glaucoma are unable to take medication as prescribed. The potential of MIGS to benefit such patients by controlling their glaucoma better (and ultimately reducing health care costs) is an important part of its anticipated value. Stakeholders consulted in the Environmental Scan mentioned that other advantages of MIGS over more invasive surgeries are seen by specialists consulted as including safer surgeries, faster patient recovery, and less need for post-operative care.[154]

A second set of facts bearing on the ethical analysis to follow is that current usage of MIGS in Canada is based on criteria that are not strongly evidence-based, standardized, or personalized to the needs of patients. It was noted in the Environmental Scan that the availability of MIGS as part of a province or facility's glaucoma treatment offerings is subject to funding for devices, hospital approval, training of staff, and availability of surgeons.[154] Not only is MIGS unevenly available across Canada, but so too is the usage of specific MIGS devices, which tend to be used according to surgeon preference, training, experience, and comfort level.[154] Moreover, the allocation of devices to patients currently proceeds without objective criteria, subject to surgeons' discretion.[154] Together, these conditions produce a situation that is notably devoid of personalized treatment for individual patients, hence, far removed from the ideal of MIGS being part of glaucoma management being tailored to the needs of individual patients. These contextual facts set the stage for the following ethical analysis.

6.2.1 Major Ethical Issues Raised by the Use of MIGS

The published literature to date contains little discussion of ethical issues relevant to MIGS. In part, this is because the use of MIGS is not seen to entail significant risks or trade-offs between benefit and harm. It is considered to be safer than more invasive glaucoma

surgery, with fewer complications and faster recovery time; hence, presents no apparent harms to be weighed against their benefits to patients.[154] Additionally, because MIGS devices are relatively new, there has not yet been time for ethical issues surrounding the context of their actual or potential use to emerge in practice and be analyzed by researchers.

Peer-reviewed literature about broader social and cultural considerations around the use of MIGS is also limited. As noted in the CADTH Environmental Scan, little published information exists on the geographical, epidemiological, socioeconomic and sociocultural, political, and legal dimensions of MIGS use in Canada, or on quantitative data on MIGS usage or costs.[154]

Drawing from information from the literature review, and the results of the clinical, economic, patients' perspectives, and implementation analysis reports, two main categories of issues capture ethical and social concerns relevant to considering the optimal use of MIGS in Canada. They are:

1. equity of access
    - equity concerns about private versus public payment for MIGS
    - equity concerns related to structural societal factors
2. the ethics of surgical innovation
    - general issues in the ethics of surgical innovation
    - adequate oversight in the context of surgical innovation
    - informed consent in the context of surgical innovation.

6.2.2 Equity of Access

The Implementation Issues Analysis and Environmental Scan reveal that specialists experienced in the use of MIGS are concerned about fair provision of MIGS surgery under conditions of scarcity and disparate health systems. Equity in access to MIGS is recognized to be a problem with current practice, given that patients in one part of a province might have no access to MIGS procedures at all while patients elsewhere in the same province might be able to choose from a range of MIGS procedures.[154]

Beyond systemic disparities in MIGS availability, there are economic ones, as well, due to the highly variable ways in which MIGS devices are paid for. Some patients must buy a device from a physician, health care facility, or through a pharmacy, while the device is free to other patients in the same province.[154] This financial burden can be compounded by the requirement for patients in remote locations to fly to urban centres for MIGS surgery, incurring significant personal costs for travel and lodging during the preoperative and post-operative periods and for follow-up consultations.

Other ethical concerns about fairness in patient access to MIGS go beyond the systemic level down to the individual level of surgeon discretion in deciding which patients to prioritize for MIGS surgery, either government-paid or self-paid. In current practice, surgeons often have a limited number of devices to allocate and use their discretion to allocate MIGS devices as they see fit.[154] This situation of personal discretion is to some extent inevitable in a content of innovation, in which the optimal use of devices is far from being clear and "early adopters" of new devices will necessarily work without formal guidance as these innovations are introduced into practice.

A more widespread use of new technology makes consistency of medical judgment important for fairness as well as quality. Many surgical specialists consulted by CADTH indicate a need for objective criteria to guide how MIGS devices are used and for which patients in which circumstances.[154] Surgeons' concerns may tend to foreground clinical criteria such as the patient's stage of glaucoma, readiness for cataract surgery, and other medical details that might be taken to determine medical need and benefit. Yet these concerns are only part of the wider picture of equity in access to Canadian health care.

As philosopher Lynette Reid notes, the concepts of equitable access to health care is more complex than it might initially appear, given that among the many potential forms of differential or preferential access, some are justifiable (or indeed optimal) while others are not.[155] Among the various forms of differential access, some are straightforwardly wrong in their principles and outcomes (such as giving preferential care on the basis of bribery or a patient's social status) and have no particular relevance to MIGS as such. More complex issues are raised by four other forms of differential access Reid enumerates:

- a context of innovation, including research and differential pace of practice improvement
- wait lists or resource allocation practices that are arbitrary or poorly organized
- situations in which some health care goods and services must be privately paid for
- structural factors affecting populations (such as geography, language and literacy, racialized identity, legacies of colonialism, and other social determinants of health).[156]

The first two axes of differential access have already emerged as being relevant in the view of stakeholders consulted for the Environmental Scan.[154] Current practice in using MIGS takes place in a context of system-wide innovation: "early-adopter" surgeons are using various MIGS devices for patients selected for surgery according to variable medical criteria, using payment methods varying by province, institution, and patient circumstance. While such differential access is unavoidable in the early stages of innovation for a new medical device, there is currently evident discomfort with the current state of affairs among many of the stakeholders consulted in the Environmental Scan. Their expressed concerns suggest that the more widespread use of MIGS has crossed over from the early-innovation stage to one in which the lack of criteria for allocation of MIGS threatens to be arbitrary and poorly organized; thus, an unacceptable form of differential treatment.

The following sections will consider each of these four axes of differential access in turn for their bearing on the optimal use of MIGS. While conceptually distinct, these topics are substantially interwoven with respect to the current practice of MIGS use in Canada and the views of ophthalmology and glaucoma specialist physicians experienced in using MIGS, so the discussion of those issues will necessarily overlap among the sections.

6.2.3 Equity Concerns About Private Versus Public Payment for MIGS

Whatever policies various jurisdictions adopt with respect to public coverage of MIGS devices, it is likely that those different policies may result in some Canadians continuing to have more access than others. Questions about equity raised by disparate funding policies for medical treatment across provinces and territories in Canada are beyond the scope of this review. Equally beyond the scope of this review are ethical concerns about the legitimacy of mixed public/private-pay funding for medical procedures in the Canadian health care system.

However, some issues about payment are specific to MIGS devices and procedures and should inform thinking by health care decision-makers about their optimal use. The foremost

one is clarity about whether and when the self-pay option is consistent with health act legislation. Many ophthalmology and glaucoma specialist physicians consulted by CADTH report that their institutions offer MIGS devices and procedures on a private-pay basis (either out of pocket or through patients' third-party insurance), but at least one respondent reports that his facility decided not to have patients buy their own MIGS devices and procedures for fear that doing so could violate federal or provincial regulations.[154] Clarity about the legality of private payment for MIGS must be the first order of business for any jurisdiction in order to begin discussions of equitable access.

A second issue of equity concerns whether and how MIGS devices and procedures are to be framed as either an optional upgrade within the current paradigm of medically adequate glaucoma management, as the majority of ophthalmology and glaucoma specialist physicians seem to consider it, or as a medically necessary treatment for some patients, as other ophthalmologists believe. Jurisdictions must decide what criteria define a medically necessary procedure, and when a procedure is not medically necessary but rather considered an upgrade over an existing procedure.[154] Each option has its difficulties for considering equitable access.

6.2.4 MIGS Viewed as an "Optional Upgrade"

Where MIGS is adopted into health systems as an option for patients to choose for self-payment, it may be seen as analogous to other technologies for eye care. In Manitoba, for instance, MIGS devices in some jurisdictions are offered for purchase by patients from physicians' offices, analogously to the sale of premium lenses offered to patients as an upgrade for cataract surgeries.[154]

The economic calculus of choosing MIGS surgery can be difficult for patients and surgeons alike to navigate. As noted in the CADTH Environmental Scan, MIGS may give a QoL benefit to patients by reducing the burden of medication and improving vision outcomes.[154] However, the cost of prescription drugs is usually covered by provincial insurance plans for patients over the age of 65 (who constitute a large proportion of patients with glaucoma), while MIGS devices and procedures usually are not, and are either bought in limited quantities by individual hospitals or are paid for by patients who can afford to do so. It is far from simple for patients or surgeons to consider the economics of either choice and balance that against QoL improvements.

Furthermore, viewing MIGS as an optional upgrade raises analogous problems to those ethicists have already identified with offering premium lenses as an upgrade for cataract surgeries. Patients with cataracts are often older, and their informed consent may be compromised by multiple factors. These include visual impairment and potential loss of independence, confusion about financial options, language or cultural barriers, and the phenomenon of "innovation bias" (or the presumption that new technology must be inherently better). As noted in a study of patients considering "premium lens" cataract surgery, *"[p]atients who misunderstand the optional nature of noninsured services may make substantial sacrifices to pay for cataract surgery. Alternatively, they may decide to postpone or forgo surgery until they can afford the noninsured costs, which will leave them to suffer unnecessarily for longer with correctable impaired vision*" (p. 814).[157] Patients with Glaucoma considering the choice of MIGS as a self-pay upgrade may face many of these same obstacles to sound informed choice.

The difficulties these circumstances create for physicians charged with ensuring patients' informed consent will be examined below under the discussion of professional ethics.

Looking at the issue from an equity perspective, however, recognition of these problems created by an ”optional upgrade” framing of MIGS also places an onus on health systems. To the extent that health systems endorse current evidence as supporting the use of MIGS as beneficial but not essential for adequate glaucoma care, they must consider how this option can best be chosen on an informed basis given the vulnerabilities of patient populations.

6.2.5 MIGS Viewed as a “Medical Need”

The opposite pole of pursuing equity in access to MIGS might seem to be for health authorities to declare the device a medical need for certain categories of patients with glaucoma who would otherwise be taking medication. As described in the Patients’ Perspectives and Experiences Review, many patients have difficulty following a complex regime of medications. For such patients it might seem (as some specialists believe) that MIGS should be seen as a medical necessity and not a premium lifestyle choice.[154]

However, the concept of medical need is itself highly contextual rather than a fixed objective standard of assessment. Lynette Reid observes that in Canada the concept of medical need is bound up with many complex questions: what level and kinds of care our public health systems are intended to provide; what standard of care is affordable for all given fiscal and political constraints; and whether individual physician judgment or a holistic and standardized systems viewpoints should determine judgments of medical need.[156] Two guiding maxims Reid notes are particularly relevant to thinking about MIGS as a putative medical need. First, *“the judgment of what constitutes good medical care is always made in light of the opportunity costs of spending money and attention on some needs rather than others”* (p.123).[156] Second, within a universal health care system such as Canada’s, which upholds the principle *“that people receive care based on need and not ability to pay,”* it is also true that *“medical need may refer to a range of acceptable solutions to prioritization problems”* (p.128).[156] The upshot of this is that the goal of providing equal access to MIGS — seen as a medical need rather than an optional upgrade — can be meaningfully discussed only in the context of the larger health care system. Rather than being the product of an individual surgeon’s judgment about an individual patient, it can only be assessed by a surgeon against the backdrop of a systemic consensus on what levels of care for which patients at which medical circumstances can be affordable for all under a public health care system.

The factors that must inform systemic reflection about medical need for MIGS will include relevant insights into the larger spectrum of treatment within which MIGS is situated as a new option. This includes understanding how specific groups of patients are or are not being successfully treated by the lower- and higher-intensity options bracketing MIGS (namely eye drops on one side and invasive surgery on the other). One aspect of this understanding involves considering what Reid describes as structural factors producing differential health care treatment (such as geography, racialized identities, and legacies of colonialism); these factors will be subsequently discussed.

There is also a more general characteristic of earlier-stage patients with glaucoma deeply affecting considerations of their medical need for MIGS, namely the fact that up to 80% of patients with early-stage glaucoma have difficulty taking a regimen of eye drop medication as prescribed.[154] Given the potential for MIGS to benefit patients’ QoL, improve disease control, and reduce costs to individuals and the health care system when used to lessen dependence on medications, there is strong reason to consider it within the framework of

publicly-insured ”medical need” coverage as opposed to being a privately-funded “optional upgrade.”

Doing so would reduce the inequality created by having those patients who can afford to do so privately paying for a surgery that has significant medical and health system benefits. On the other hand, declaring MIGS a medical need for all patients taking glaucoma medication would fail to distinguish between those patients who are more or less able to use eye drops as prescribed and hence are more or less acutely in need of an alternative mode of glaucoma management. For this reason, neither the “optional upgrade” nor the “medical need” paradigm for MIGS is likely to suit all patients well.

6.2.6 Equity Concerns Related to Structural Societal Factors

Equity Concerns Related to Geography

The 1985 Canada Health Care Act declares *“that the primary objective of Canadian health care policy is to protect, promote and restore the physical and mental well-being of residents of Canada and to facilitate reasonable access to health services without financial or other barriers.”*[158] However, the enormous scale of Canada’s geography and the distribution of its citizens across rural and remote areas, as well as more densely populated ones, means that parsing ”reasonable access” and “financial or other barriers” must inevitably take geographical realities into account.

Canada’s Health Care Act makes no substantial comment on the relative quality of care that can be reasonably expected by residents of the country’s rural and remote areas as opposed to more densely populated ones.[158] From a pragmatic perspective, this omission is understandable, given the extensive economic, practical, and other policy issues at stake when providing health care in remote and rural regions. However, the challenge of promoting equity in the optimal use of a medical technology such as MIGS is much complicated by the lack of principled guidance.

As noted in the Environmental Scan, most rural and remote areas of the country do not have centres that offer MIGS devices and procedures (or Trabeculectomy) as an option to patients; therefore, any patient that is a candidate for surgery will be referred to an ophthalmology and glaucoma specialist physicians, usually operating out of a larger urban centre. One surgeon who commonly operates on patients referred from the Yukon reported that not only does the territory have a high prevalence of glaucoma but the region’s lack of specialists means that patients are often referred too late in their disease progression for MIGS procedures to be a useful treatment option.[154] Such patterns likely hold true as well for regions of Canada that are not remote but rural, where travel to urban centres is viable but potentially difficult and costly. A recent study of regional variations in eye disease detection and treatment in Prince Edward Island finds that that factors such as “travel times, absence from work and travel costs to the clinic”[159] (p. 273) are likely responsible for geographic disparities across the province in the use of eye care and in eye disease detection and treatment. Patients living farthest from urban clinics access eye care at lower levels, leading to poorer medical outcomes.[159]

Such unequal patterns of eye care access, diagnosis, and treatment are particularly regrettable with respect to MIGS given its potential to be distinctively beneficial for patients in rural and remote locales. Because MIGS typically requires few or no post-operative specialist visits, its use could avoid the time, difficulty, and out-of-pocket expense that

patients would otherwise incur for follow-up visits to ophthalmology and glaucoma specialist physicians after traditional invasive surgery.

This suggests that prioritizing the use of MIGS for patients living in rural and remote regions is a possible approach to seeking equity in glaucoma treatment. More standard policy responses to unequal access to care and outcomes for patients with glaucoma emphasize removing barriers to receiving care and treatment by seeking ways for patients to access care more readily. This is difficult to achieve practically and economically, however, and bringing more specialized MIGS surgeons into remote and rural areas is unlikely to happen. For this reason, identifying rural or remote residence as a preferential indication for MIGS use may also be a sound policy approach. Those responsible for formulating clinical practice guidelines or criteria for MIGS may wish to focus on geography as a criterion for optimal MIGS use.

Equity Concerns Related to Racialized Identities

A second important structural factor to consider with respect to equity in access to MIGS is the demographics of Canada's population with respect to racialized and ethnic groups, their distinctive risk factors for glaucoma, and the way in which societal relationships may affect their interactions with health care systems in general and glaucoma specialists in particular.

Recent studies in the US have found that populations of African and Latino ancestry appear to have a higher risk of OAG and worse medical outcomes during the disease course, with African Americans being three to four times more likely to be diagnosed with glaucoma than white people.[160,161] African Americans develop glaucoma at a younger age, suffer more rapid disease progression, and are nearly seven times likelier to go blind from glaucoma than non-Hispanic caucasians.[162] The prevalence rate of glaucoma for Latinos is similar to that for African Americans.[161]

Importantly, the reasons for these differences are unknown, and are the subject of debate among researchers who disagree about the relevance of potential genetic factors as opposed to socioeconomic ones.[163] Among African American populations in the US, research showing the prevalence of glaucoma, barriers to diagnosis and effective treatment, and worse post-surgery outcomes in black patients compared with whites have been studied mainly in socioeconomically disadvantaged urban East Coast populations such as Baltimore[164] and Philadelphia.[165] How much emphasis to put on racialized identities and genetic factors as opposed to social, economic, and cultural ones in understanding and countering health inequities is itself a controversial topic.

Nonetheless, continuing to target interventions and research at racialized groups seems justifiable and necessary at present. In response to identified socioeconomic factors posing barriers to access (including lack of trust for medical professionals resulting from historical legacies of injustice), ophthalmological research centres have tried public health approaches to reach populations at high risk of glaucoma in community-based settings.[162] The same need to consider racial differences and disparities holds true of research on glaucoma surgeries. As Taubenslag notes:

"[U]ntil better genetic markers for surgical prognosis come along, we cannot ignore surgical outcomes disparities that fall along the lines of bio-social groups. Reviewing these disparities hopefully encourages providers to approach glaucoma surgery for their Black patients with the care, deliberation, and counseling this high-risk group deserves. There is a need for further study of racial disparities for all of the discussed procedures. This is especially true for… the new minimally invasive glaucoma surgeries (MIGS)… It is important

to collect data on these ab interno procedures to determine whether they should figure more prominently in the treatment algorithm for Black patients or for other high-risk groups" (p.390).[165]

In order to advance such data collection and to improve the quality of care for all demographic groups of patients, in March 2018 the American Glaucoma Society awarded a research grant to *"study how often minimally invasive glaucoma surgery (MIGS) devices and procedures are used in black and Latino glaucoma patients and whether these devices perform similarly across races, ethnicities, genders, ages, and regions."*[166] One of the challenges this project will have to grapple with is the widespread underrepresentation of non-white groups in medical research, grounded in historical mistrust. African-American subjects studied who declined to participate in a recent Primary Open-Angle African American Glaucoma Genetics project *"were primarily distinguished by their discomfort in providing DNA for research studies,"* and other studies have similarly *"cited mistrust in research as the most commonly identified barrier to study participation among African Americans"* (p.7).[98]

As yet it is unknown what bearing these factors identified in US populations have for racialized populations in Canada. It is virtually certain that continuities and parallels do exist, however, and must be taken into account in considering optimal MIGS use in this country. One of the few published comments on this topic notes the need *"to review and track data specific to the Canadian population toward guiding decisions regarding glaucoma screening, treatment, and public health related strategies, taking into account demographic shifts due to immigration from Asia, the Middle East, and Africa"* (p.5).[7]

Such considerations are particularly important to adapt to the circumstances and needs of Canada's Indigenous populations in order to honour this Call to Action by the Truth and Reconciliation Commission (2015): *"In order to address the jurisdictional disputes concerning Aboriginal people who do not reside on reserves, we call upon the federal government to recognize, respect, and address the distinct health needs of the Métis, Inuit, and off-reserve Aboriginal peoples."*[167] In these populations, potential genetic factors combine with common comorbidities, remote and rural residence, and histories of injustice in relationships with medical establishment to create a distinctive context for approaching glaucoma prevention, research, and treatment. Equity demands that guidelines for the optimal use of MIGS include appropriate clinical, policy, practice, and research dimensions.

6.2.7 The Ethics of Surgical Innovation

In contrast to the concerns about equity in access to MIGS that are primarily the responsibility of health care systems to address, another set of ethical issues bears on the responsibilities of medical professionals (and their professional organizations). As has already been noted, MIGS devices and procedures are relatively new and now take many different forms whose comparative and collective benefits have not yet been clinically established. The practical upshot for ophthalmologists treating glaucoma, therefore, is *"an abundance of available MIGS devices and procedures, with little guidance as to which patients will benefit from one device over another."*[168]

Many of the ethical challenges that this context poses for considering the optimal use of MIGS are framed within the existing literature on the ethics of surgical innovation. This field, part of the larger area of health care ethics, analyzes ethical hazards and responsibilities bound up with the development and use of new surgeries and medical devices. The bulk of this literature focuses on surgical innovation, but many of the concerns raised extend also to

innovative medical devices. In a 2016 systematic review of published work on the ethics of surgical innovation, researchers identified four major themes: i) the need for oversight of the use of novel surgeries in order to promote patient safety and evidence-based treatment alongside innovation; ii) ensuring that patients give informed consent to treatment decisions; iii) the learning curve for surgeons devising and practising new techniques on patients; and iv) challenges of treating vulnerable patient groups.[169] The following discussion will outline how these general themes in the ethics of surgical innovation bear on the optimal use of MIGS using the two broad analytic categories of "oversight" and "informed consent."

Adequate Oversight in the Context of Surgical Innovation

As with any innovative procedure or device that early-adopter surgeons invest time in learning to use and build into their practice as a specialty, MIGS presents the ethical risk of personal investment inappropriately influencing clinical judgment to the detriment of patients' welfare. The larger literature on conflicts of interest in the context of surgical innovation identifies multiple sources of conflict. At a most instrumental level, there can be reputational and financial benefits at stake in developing, testing, and using a new procedure.[170] This may include relationships with a device manufacturer that might undermine objectivity in assessing the benefits of a specific innovative device (either over traditional treatments or in relation to other innovative devices) and its suitability to individual patients. The potential for such conflicts can affect not just individual clinicians but also institutions such as universities and hospitals: *"institutions may depend on funding from device manufacturers and seek to cultivate a reputation for being at 'the cutting edge,"* potentially leading to *"the pursuit of innovation despite risk to patients and in the absence of adequate evidence to support its use"* (p.11).[171]

All of these potential sources add up to an overall fault in judgment by surgeons and institutions known as "optimism bias": *"a tendency to overestimate the positive effects of an innovation, which thereby contributes both to difficulties in evaluating the effectiveness of innovation and to widespread uptake of procedures with poorly understood outcomes"* (p. 10).[171] Put more concretely, when surgeons or institutions are professionally invested in a new procedure, they tend to want to use it and to see clinical evidence of benefit, and this motivation can lead to advocacy or recommendation of a new procedure that might not be made by specialists less invested in that option.[170]

The literature on innovation-related conflict of interest notes that remedies to prevent and mitigate conflicts must involve stakeholders including surgeons, regulators, hospitals, and patients. These measures include transparency by surgeons and institutions in acknowledging all potential conflicts, institutional oversight in granting privileges for innovative surgeries, and candid discussion with patients.[172-174]

Beyond oversight focused on conflicts of interest, another important kind of oversight relevant to the optimal use of MIGS concerns the responsibility of all stakeholders to ensure that use of an innovative device is guided by clinical evidence as extensively and as soon as possible.

Achieving this in turn requires that as an innovative device is introduced into the market and taken up by "early-adopter" surgeons, its usage and outcomes are tracked, evaluated, and reported so that its optimal usage be impartially assessed. Discussions of the ethics of surgical innovation recognize this as part of the ethical responsibility of stakeholders involved in the introduction of new devices or techniques.[175,176]

Following through on this commitment takes individual and organizational resources; however, and it is unclear whose responsibility it is to ensure that all uses of MIGS in Canada are tracked. Clarifying where this responsibility lies will be itself an ethical requirement for surgeons, their professional bodies, and health care institutions.

Informed Consent in the Context of Surgical Innovation

A final topic from the literature on the ethics of surgical innovation of specific relevance to the optimal use of MIGS is that of informed consent. The responsivity of surgeons to ensure that patients are fully informed of the risks and benefits — and the broader advantages and disadvantages — of a particular treatment for their disease is of course part of all clinical ethics. Given the particulars of MIGS as an innovative technology taking many forms with little clinical evidence as yet, carrying out this responsibility has distinctive challenges.

One of these challenges has to do with whether surgeons fully inform patients of the diversity of MIGS options and the paucity of clinical evidence about their effectiveness.

With respect to the first question, the ethics literature on surgical innovation takes it as axiomatic that surgeons are professionally obligated to fully disclose factors relevant to patients' capacity for informed choice, including the uncertainties and unknowns associated with innovative procedures.[176] A 2016 systematic review of this literature enumerates an interrelated list of items seen as necessary for surgeons to disclose to patients, the innovative nature of the procedure, the surgeon's experience performing it, risks and benefits of the procedure (including possible and unknown risks or outcomes), as well as the available evidence, and alternative forms of treatment.[169]

In the context of MIGS usage in Canada, in which individual surgeons seem to be offering patients just one or a few in a wider and evolving terrain of MIGS devices on the market, patients should be fully informed of this scenario and of the paucity of comparative evidence. To be sure, this information is unlikely to expand meaningful choices for patients inasmuch as they lack any likelihood of or basis for "comparison shopping" among the devices or among surgeons. Nonetheless, transparency about these circumstances must be provided by surgeons to patients with glaucoma considering MIGS as a treatment option.

Another challenge — one that harkens back to previously discussed issues of equity — concerns an arguable responsibility of surgeons to take a more expansive view of what patients need for informed choice bearing on MIGS. On this more expansive view, informed choice encompasses not just clinical factors, per se, but a broader set of individual factors bearing on this choice of treatment. Such relevant information might include vulnerabilities such as old age, geographical location, and capacity to pay non-insured or out-of-pocket costs associated with choosing MIGS compared with other treatment options.

The reason why such factors may need to be simultaneously considered in the context of MIGS can be extrapolated from comments by McAlister et al. on surgeons' responsibilities for informing patients about options for cataract surgery when self-pay options for premium lenses are available:

"Ophthalmologists providing noninsured services should consider the potential harm of financial burden on a vulnerable patient with cataracts…. [and must provide patients with] the information they need to make informed decisions about their medical care... [P]hysicians should not misrepresent medically necessary and unnecessary services when both insured and noninsured options exist. This is particularly true for patients with cataracts, given the potential added vulnerabilities of these patients" (p.814).[157]

Applying to the context of MIGS, these ethical principles imply that surgeons discussing this treatment option with patients must explore the financial and other personal costs associated with MIGS as opposed to other treatment options for glaucoma. For patients who live in remote or rural areas, for example, costs associated with travel for surgery and follow-up visits will have to be factored into the physician–patient discussion in order for patients to make fully informed decisions.

If the scope of physicians' professional responsibility to enable informed consent is construed in this expansive way, the upshot is a highly complex picture of what surgeon–patient discussions must encompass. Just how broad and detailed the surgeon–patient consultation must be in order to enable informed consent will be subject to further debate—but however construed, ensuring that this responsibility is carried out well must be a concern not only for glaucoma specialists but also for their professional bodies and other health care stakeholders.

6.3 Summary of Results

Findings about the optimal use of MIGS from an ethical, social, and cultural perspective fall within two normative categories: *equity* (concerning the goal of ensuring a fair societal distribution of access to MIGS) and *professional conduct in the context of surgical innovation*.

Within the equity category, ethically and socially relevant issues include the need for guidelines to help institutions and specialists fairly allocate MIGS under conditions of scarcity; concerns about public coverage versus private payment for MIGS; diverging views of MIGS as an "optional upgrade" or a "medical need;" concerns about equitable access to MIGS for patients living in rural and remote locations; and uncertainty about the clinical and social factors that should be brought to bear on determining the optimal use of MIGS for certain racialized groups.

With respect to the context of surgical innovation, ethical concerns include conflicts of interest arising from some institutions' and professionals' incentives to recommend the use of specific MIGS devices to patients; the need to have clear assignment of responsibility for tracking and reporting outcomes of MIGS usage; and challenges in conceptualizing and putting into practice the responsibility to ensure patients' informed consent with respect to the potential use of MIGS.

7. Implementation Issues Analysis

This section addresses the following research question:

Research Question 9:	How is glaucoma managed across jurisdictions and what is the current availability and use of MIGS devices and procedures in the treatment of adult patients (over 18 years) with glaucoma?

The implementation section that follows was informed by data and analysis from the CADTH Environmental Scan report titled *Minimally Invasive Glaucoma Surgery: Implementation Considerations*.[154] The objective of this Environmental Scan was to identify and summarize information regarding the current practice and the implementation of MIGS devices and procedures in Canada. The following research questions from the Environmental Scan[154] were used to inform the Implementation Issues Analysis for MIGS devices and procedures:

1. How is glaucoma managed across jurisdictions and what is the current availability and use of MIGS devices and procedures in the treatment of adult patients (over 18 years) with glaucoma?
2. What are the relevant factors to consider if implementing MIGS devices and procedures in a jurisdiction (across urban, rural, and remote settings) for the treatment of adult patients with glaucoma?
3. What are the challenges and enablers impacting the use of MIGS devices and procedures in Canada for the treatment of adult patients with glaucoma?

At the time of publication of the Environmental Scan (May 2018), the CyPass Micro-Stent was still part of the global market and had not been voluntarily withdrawn. Therefore, the Environmental Scan on which this section is based on included the CyPass Micro-Stent as a treatment option, as this was the landscape of MIGS at the time of publication.

7.1 Methods

This report is a narrative summary of the implementation issues related to MIGS devices and procedures in the Canadian context and was prepared by one reviewer using data and analysis from the previously published Environmental Scan report.[154] The following description of methods presents those used by the Environmental Scan; further details can be found in the full report.[154]

The Environmental Scan used a two stage approach performed concurrently to understand implementation issues associated with MIGS devices and procedure. Stage one involved consultations with key stakeholders (informants). In stage two, data from a review of the published and grey literature were extracted. These data were then used to supplement the data gathered from consultations.

Consultations were conducted with key informants identified through the clinician networks managed by the CADTH Implementation Support and Knowledge Mobilization team or referred through other informants during consultations. The key informants were consulted to provide a general overview of policy, practice, and implementation issues related to MIGS, as well as to identify additional relevant literature.

A semi-structured interview guide was developed to guide the consultations. The interview questions were based on the research questions and were related to the types of MIGS

devices and procedures available, challenges and enablers to the use of MIGS, and implementation considerations. Consultations took place between October and December 2017. Consultations were conducted by phone by a CADTH Knowledge Mobilization Officer. The interview questions can be found in the published Environmental Scan report.[154]

Stakeholder feedback was solicited by posting a draft version of the Environmental Scan report[154] on CADTH's website and by emails to subscribers to CADTH's mailing lists. Key informants involved in the consultations were also asked to provide feedback. Stakeholder feedback was be used to supplement information received from the consultations and literature search.

The literature search was performed by an information specialist, using a peer-reviewed search strategy.

Implementation-related information was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates; and Embase (1974–) via Ovid; CINAHL (1981–) via EBSCO; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were glaucoma, minimally invasive glaucoma surgery, and minimally invasive glaucoma surgical devices.

Methodological filters were applied to limit retrieval to studies relevant to implementation issues. The search was also limited to English-language documents published between January 1, 2000 and October 17, 2017. Regular alerts that were established to update the search were run until September 2018.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, systematic review repositories, economics-related resources, public perspective groups, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

7.1.1 Selection Criteria

English-language reports that described implementation and context issues, including challenges and enablers associated with treatment of glaucoma with MIGS, were eligible for inclusion. All study designs and report types were eligible for inclusion.

Dates were not limited beyond the initial literature search limitations (January 1, 2000 onwards) and were not limited by country of origin.

7.1.2 Selection Method

Results from the literature searches were screened independently in a two-step process by one reviewer for information related to implementation issues in Canada. First, titles and abstracts were screened to identify potentially relevant papers. Next, full-text articles were screened for eligibility. Ineligible or irrelevant reports were not included in the review.

7.1.3 Data Analysis Methods

Data extraction was performed by one reviewer. From each potentially relevant article, one reviewer extracted bibliographic details (i.e., authors, year of publication, and country of origin) and data relating to barriers and facilitators. The extracted data were organized in Microsoft Word tables under headings based on the INTEGRATE-HTA Context and Implementation of Complex Interventions (CICI) framework.[177]

These data supplemented the information provided by consultations and attempted to address potential information gaps.

7.1.4 Descriptive Analysis

Data from consultations and findings from the literature were sorted into categories based on the implementation and context domains identified by the CICI framework.[177] This framework identifies and examines the influence of context and implementation factors that enable or limit uptake of an intervention, including how these factors affect the population reach and effectiveness of an intervention.

Context within the framework refers to a set of characteristics or circumstances that interact, influence, modify, facilitate, or constrain the intervention and its implementation. Implementation, for the purposes of the framework, is considered to be an actively planned and deliberately initiated effort with the intention to bring a given object into policy and/or practice.[177]

Using this framework, the domains of context, socioeconomic, sociocultural, setting, political, legal, geographical, ethical, and epidemiological, were used to guide the categorization of data on challenges and enablers of implementing MIGS across Canadian jurisdictions. The four domains of implementation (provider, organization and structure, policy, and funding), as well as the additional domain of patient, were used to further guide the categorization of identified challenges and enablers as they relate to the implementation of MIGS devices and procedures across various levels of health care service delivery.

7.2 Results

The results presented below, unless otherwise specified, are drawn from the CADTH Environmental Scan *Minimally Invasive Glaucoma Surgery: Implementation Considerations*.[154]

7.2.1 Consultations

In total, 21 key informants were interviewed for the purposes of the Environmental Scan.[154] This included 18 ophthalmology and glaucoma specialist physicians and three health system administrators. Of these key informants, six serve as current, past, or incoming presidents of national professional bodies in the ophthalmology and glaucoma specialty communities.

Efforts were made to contact stakeholders in every province and territory, and responses were received from Yukon, British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Newfoundland and Labrador, and Prince Edward Island.

Informants also provided additional information that was not available in the literature, such as information regarding the impact of geography and setting on MIGS implementation.

Unfortunately, no information from either the consultations or literature was available to comment on socioeconomic, sociocultural, political, legal, or epidemiological domains of implementation.

7.2.2 Literature Search

The literature search yielded 1,026 citations, of which 19 studies were determined to be eligible to address the research questions for the Environmental Scan.[154] One article was added after suggestion by a stakeholder during the Environmental Scan stakeholder feedback period.[178] One article was added during a monthly update of the literature search.[179] In total, 21 articles were used to inform the Implementation Issues Analysis.

Eight articles were published in Canada,[13,19,152,168,178-181] nine articles were published in the US,[32,182-189] two articles were published in the UK,[126,190] and one article was published in Saudi Arabia.[191] One article was written by a Canadian surgeon, but contained information relating to use of MIGS in the US.[31] Two articles were systematic reviews,[168,181] and six articles were narrative reviews.[13,126,187-189,191] Two articles were surveys, one of UK glaucoma specialists and their preferences for glaucoma surgery,[190] and the other of Canadian ophthalmologists and their perspectives on the gelatin microstent,[179] and one article was a retrospective review of billing service claims to analyze trends in glaucoma procedures.[180] Additionally, one article was a cost comparison of Trabectome, iStent, and ECP to glaucoma pharmacotherapy.[19] The remaining eight articles were news articles, summaries of proceedings, or editorials.[31,32,152,178,182-186]

7.2.3 Availability of MIGS Devices and Procedures and Funding Options

Funding issues emerged as one of the most pressing barriers to implementation of MIGS devices and procedures in Canada.[154] Currently, MIGS devices or procedures are not listed as an insured service in most Canadian provinces and territories, with the exception of Alberta and Quebec. Currently, decisions on whether to fund MIGS and which MIGS device or procedure to fund or purchase are solely up to the discretion of the specific facility providing the services. Given that facilities have a finite budget that must be distributed among the services they offer, without additional funding for MIGS devices and procedures these costs must be absorbed into the existing budget, or absorbed by the patients themselves. This means that in the majority of Canadian provinces and territories, patients either pay out-of-pocket and/or the facility covers the cost of MIGS devices and procedures.[154]

Health system administrators are pressured to both cut costs and simultaneously offer new technologies and services. Many health care systems are moving toward a “cost-based” model, where cost analyses become important in the decision-making for treatment decisions, but these in-depth analyses are currently lacking for MIGS devices and procedures.[19] Similarly, some organizations also have a policy in which a “business case” for new technologies must be presented to a committee — this may limit the availability of MIGS within individual facilities but can help facilities add a level of control over growing costs, and can help to manage pressure from industry sales strategies. Facilities can also seek approval for funding for devices and associated capital costs from other sources, such as the hospital’s foundation, yet these may be affected by equipment budget cycles. Although a barrier to the use of MIGS is the prohibitive start-up costs for some procedures or devices,[186] discounts can be negotiated with manufacturers off the initial capital investment if devices are continuously purchased by a facility.[192] Furthermore, within those facilities that provide MIGS devices and procedures, there can be few MIGS devices

available due to limited funding. This creates the potential for increasing wait lists for this surgery. Current hospital funding models were identified as a barrier to accessing MIGS in a survey of Canadian opthalmologists.[154,179]

Some facilities are offering MIGS to those patients who can pay an additional fee, similar to the “lens upgrade” fee that is in place for cataract surgery. This introduces ethical issues relating to health care being only available on the basis of ability to pay as opposed to need. Facilities and providers are therefore hesitant to offer MIGS as an out-of-pocket expense, especially as many glaucoma specialists consider MIGS to be a medical necessity and not an upgrade or “premium” choice. Related, as provinces will often cover the costs of glaucoma medications but not MIGS, patients not able to pay out of pocket for MIGS will continue using medications to control their glaucoma. These patients risk having their glaucoma advance, and once progressed too far, they may no longer be a candidate for the surgery and instead face more invasive and riskier surgeries to continue their glaucoma management.[154]

There is also the option for some regions to send patients to alternate facilities that can provide MIGS devices and procedures. Sending patients out of area or out of province can be costly to the health region. While some provincial regions, such as Ontario’s Local Health Integration Networks, may have agreements between one another to cover costs borne from sending patients to other areas, more often, provincial regions may be unable to recuperate the costs of MIGS provided by another region. In some cases (for example, in the North) it is more cost-effective to send ophthalmologists from more populous regions to more remote areas to provide services on a short-term basis. This allows patients who might not otherwise receive these services to receive treatment for glaucoma, or to be referred to receive treatment; yet, given the technological requirements of MIGS, not all facilities will be equipped to provide MIGS.[154]

Because MIGS devices and procedures are not an insured service in the majority of provinces and territories and are therefore not included in the physician’s schedule of benefits, providers of MIGS must use proxy fee codes that approximate the time, complexity, or cost of MIGS devices and procedures. If there is no suitable proxy billing code, physicians may be forced to bill for procedures that are either more expensive, or take longer than the typical MIGS surgery. The lack of guidance on which proxy codes are the most appropriate for MIGS can be a barrier for use, and the lack of fee codes makes estimation of the true prevalence of use and the costs associated with MIGS difficult.[19]

7.2.4 Organization: Leadership, Structure, and Operating Room Time

Ophthalmology leadership and support within facilities are vital to facilitate the use of MIGS.[154] Commitment and contributions of ancillary staff can also contribute to the success of MIGS devices and procedures in facilities.[184] OR managers and leaders who look favourably on both ophthalmology and the addition of new technologies in the OR are advantageous for implementing MIGS devices and procedures. Leadership of these individuals can aid in persuading budget managers and administration to provide funds for new technologies and advocate for the devices and procedures in their facility. Additionally, having well-regarded leaders in ophthalmology, a strong glaucoma team, specialized staff, a large volume of patients, and a dedicated ophthalmology OR are facilitators to the use of MIGS within facilities. These facilitators may be of interest to industry and manufacturers, who can provide additional devices, training, or support for MIGS. Ophthalmology units with a dedicated glaucoma team may also have a dedicated glaucoma budget, and a dedicated OR that does not compete with other specialties for OR time. Limitations on OR time is a

potential barrier for MIGS devices and procedures, as additional surgeries such as MIGS add to backlogs and wait lists for patients. On the other hand, MIGS devices and procedures are highly standardized and can be added on as an adjunct to cataract surgery as the additional time to perform this procedure would be minimal.[186] This means that some types of MIGS can potentially be faster than traditional surgeries, increasing the total number of surgeries that can be performed and the number of patients treated.[188] However, the efficiency of the devices and procedures are also impacted by the costs of the procedures, as previously stated, and not the timing alone.[154]

7.2.5 Ethical and Policy Issues: Guidelines, Affordability, and Access

Variability in access to MIGS devices and procedures may have contributed to less understanding of the optimal use of MIGS devices and procedures and their role in the treatment paradigm.[168] In addition to the ethical issue of unequal access to MIGS devices and procedures due to affordability, the absence of solid data or guidance on the appropriate patients to receive MIGS can also raise ethical considerations, further explored in the Ethical Issues Analysis in this report. Given that there is no formalized list of indications for MIGS, facilities and institutions providing MIGS are creating their own eligibility criteria for patients, which may potentially include patient factors that do not reflect actual appropriateness for the surgery but may be based on factors including ability to pay.[154]

7.2.6 Guidelines

There is a lack of guidance or formal policies in place for the use of MIGS device and procedures and limited acknowledgement of them in clinical practice guidelines.[168] In a study of the methodological quality of glaucoma clinical practice guidelines, only three of the 11 identified guidelines mentioned MIGS as a treatment option.[168] Additionally many clinical practice guidelines, including Canadian clinical practice guidelines, are out of date. The Canadian Ophthalmologic Society (COS) guidelines[3] were last updated in 2009 and also do not mention MIGS as a treatment option. This is a contributor to barriers in use, as policy-makers rely on guidelines to see the current landscape of glaucoma management and to guide decision-making.[168] However, the Canadian Glaucoma Society published a position statement more recently in 2017, endorsed by COS, which supports the use of MIGS devices and procedures and highlights the benefits and indications for MIGS in glaucoma treatment.[193] This position statement emphasizes the agreement among many Canadian and international glaucoma specialists regarding the potential use of MIGS for glaucoma, especially for indications such as patients undergoing cataract surgery, patients unable to tolerate pharmacotherapy, and patients with uncontrolled IOP who do not clearly require more invasive options. As of December 2017, the CGS and COS therefore support MIGS as an alternative treatment option for patients with mild-to-moderate glaucoma.[193]

7.2.7 Setting and Geography: Access to MIGS Devices and Procedures

As previously mentioned, one of the greatest barriers to implementation of MIGS devices and procedures in Canada is the issue of access.[154] Currently, access to these specialized services varies widely — one facility may provide a particular (or multiple) MIGS device or procedure, and another may have no access to MIGS. A survey of Canadian surgeons found that 70.6% of respondents agreed that gaining access to some MIGS (XEN-45) is challenging.[179] The setting in which these procedures are performed also influences how many MIGS devices and procedures are available to physicians, as some facilities are specialized in eye care, including glaucoma treatments. These specialized facilities may

have a greater focus on glaucoma care than other facilities and have access to specialized eye care teams and nurses. They may also have a specific budget for MIGS devices and procedures that is not shared among other fields within the centre or hospital.[154]

Canada's considerable geographical size produces unique barriers for caring for patients with glaucoma living in more rural or remote areas. Based on information from consultations, these patients often have less access to MIGS devices and procedures, and they may be referred to receive surgical interventions much later in the glaucoma treatment pathway compared with patients with living in more urban areas. Often, these referrals to surgical interventions occur too late in their glaucoma disease progression, when the patient is no longer eligible for MIGS. With only the more invasive surgical options remaining, these patients may risk facing more advanced glaucoma and greater harms from more invasive surgeries, all a result of limited access to potential care options.[154]

Relatedly, challenges exist for caring for patients with glaucoma who live in smaller communities or in less populous provinces and territories. Fewer specialized facilities, fewer trained surgeons with experience in MIGS devices and procedures, and potential difficulties in attracting these trained ophthalmological surgeons to the smaller provinces all present as challenges. Despite these challenges, there are potential advantages to being in a smaller province, as costs may be more easily contained and applications for funding for devices more easily approved. Being part of a smaller hospital with a supportive administration may also facilitate approval of devices and procedures.[154]

When referred to receive MIGS devices or procedures, facilities that are at a greater distance from a patient's home can also create a barrier to implementation. Travelling to receive MIGS and for post-operative visits can be both time-consuming and costly for patients. These extra costs can include transportation, accommodation, and time taken off work, as well as possible lost productivity for both the patient and any potential caregivers. However, one facilitator of MIGS is that they may require fewer post-operative visits in total. This potentially makes MIGS more attractive than other surgical glaucoma management strategies for patients who live far away from a facility.[154] Surgery choices may therefore be influenced by the potential of MIGS devices and procedures to reduce post-operative care burden.[190]

7.2.8 Provider: Training, Education, and Adoption of MIGS[154]

Two significant factors influencing the uptake and implementation of MIGS devices and procedures in Canada are the training or education that providers receive, and the willingness of providers to adopt MIGS into their practice.[154]

With the rise in use of MIGS devices and procedures in Canada, medical educators will need to train residents in the use of these new technologies.[194] Currently, manufacturers provide the majority of training for MIGS devices and procedures in Canada, which helps support the adoption of their devices.[154] Training can be in the form of wet labs, videos, and supervision during surgery by a company representative. Ophthalmologists can also participate in fellowships or participate in peer-to-peer learning groups, in which they shadow or are taught by another surgeon. Although there is training available for ophthalmologic surgeons in MIGS, as the surgery is performed by a team, nurses and other staff who are involved in the procedure require MIGS training, as well. Some of this training of auxiliary staff can be provided by manufacturers in addition to the training provided to the surgeons. However, even with the availability of training, there is still a lack of trained surgical ophthalmologists in Canada (and similarly in the US)[186] to perform MIGS

procedures and insert MIGS devices. Although there are a lack of surgical ophthalmologists, general ophthalmologists and cataract surgeons may be able to also perform MIGS surgeries and fill this provider gap.[186]There is also a lack of training standards or formal credentialing for surgical ophthalmologists in MIGS devices and procedures. The lack of trained surgical ophthalmologists and credential standards can be a barrier for implementation. A facilitator to the use of MIGS devices and procedures is the expectation by new graduates to have training in MIGS.[154] Many new ophthalmology graduates have received training in MIGS; however, some academic centres without access to MIGS devices or procedures may receive less training on MIGS, and greater training on more invasive surgeries. Despite this, younger ophthalmologists may be more willing to adopt MIGS into their practice. It was suggested by consultations that the reluctance for adoption from some surgeons may stem from being later in their careers. After many years with good outcomes of more traditional surgeries, such as Trabeculectomy, they are content with continuing to use those surgeries in their practice. Some providers may not adopt MIGS because the surgery lies outside of their comfort zone.[178,190] However, one survey conducted of experienced Canadian ophthalmologists found that the majority of surgeons surveyed (70.6%) were comfortable with the procedure for the iStent, and that this was the most commonly used MIGS device or procedure.[179] Despite consultations hinting at a potential reluctance for implementation by some surgeons, 100% of those surveyed stated that they would want to incorporate the XEN-45 gelatin microstent into practice.[179] It was also noted that MIGS devices and procedures do have a considerable learning curve associated with them, as they differ from traditional surgeries, and require challenging technical abilities to perform.[178,186-188] Although the learning curve has been noted, specific descriptions of the individual learning curves of each MIGS procedure are not available.[179] However, one advantage of MIGS is the relatively less challenging nature of the surgery when compared with the Trabeculectomy.[190] The experienced surgeons agreed or strongly agreed that gaining proficiency with ab interno microstents (XEN-45) was easier in comparison to Trabeculectomy (94.1%), Ahmed glaucoma valve (82.3%), and Baerveldt glaucoma valve (86.7%).[179] Despite this, some hospitals and surgeons may be more reluctant to adopt MIGS devices and procedures as they are waiting on longer-term and higher quality safety, clinical-, and cost-effectiveness data. Nevertheless, the increase in articles and the rapid growth of companies that specialize in MIGS devices does illustrate the interest and enthusiasm in the MIGS space by analysts and investors.[183] The effect of the withdrawal of the CyPass Micro-Stent on provider acceptability is unknown at this time, but in the included survey of Canadian surgeons, only 5.9% of the 17 respondents had experience with the micro-stent, in comparison with 83.3%, 11.8%, and 17.6% of surgeons having experience with iStent, Hydrus Microstent, and gonioscopy-assisted transluminal trabeculotomy, respectively.[179]

7.2.9 Patient: Acceptance and Safety

Based on consultations, MIGS devices and procedures appear to be readily accepted by patients with glaucoma, and many patients are willing to undergo the procedure or request it as an option for their glaucoma treatment.[154] As the ineffective use of pharmacology is one of the biggest challenges in glaucoma management, MIGS devices and procedures may provide eligible patients with a means to reduce medication burden and improve their QoL. Patients may consider the relatively lower risk of the surgery, the short recovery time, and the quick return to work as factors in their acceptance of MIGS as a surgical intervention. However, given the limited availability of MIGS, the burden of travelling for surgery and follow-ups is great for many patients and may influence their decision or ability to undergo

MIGS.[154] Additionally, the potential effect of the market withdrawal of CyPass Micro-Stent on patient acceptability of MIGS is unknown.

7.3 Summary of Results

There are numerous barriers and facilitators to the implementation of MIGS in Canada. One of the major barriers relates to the issue of access to MIGS for patients within facilities treating glaucoma. Funding challenges, high start-up costs and finite budgets for facilities with the ability to provide MIGS devices can be prohibitive to their implementation. Contracts can be negotiated with manufacturers to help alleviate some of these costs, but often the costs of MIGS are passed to the patient, who must pay out of pocket for the device or procedure.

The setting in which these surgeries occur is also an important facilitator or barrier to use. Having strong ophthalmology leadership and ORs that favour new technologies such as MIGS can be an enabler to their use and an enabler for acquiring funding. Facilities that are specialized in glaucoma care may also have a specific budget for devices and procedures such as MIGS, or may be more able to attract glaucoma specialists and manufacturers to their facility. Smaller facilities, while not having these advantages, may have an easier time approving devices and contain costs more easily.

Manufacturers currently provide the majority of training opportunities for physicians in Canada, but there are opportunities for ophthalmologists to participate in fellowships and peer-to-peer learning groups to learn about MIGS. More recent ophthalmology graduates have an expectation to learn about MIGS devices and procedures, and are often more willing to incorporate MIGS into their practice. Unfortunately, even with these enablers, there is a lack of trained ophthalmologists and credential standards in MIGS, and some ophthalmologists are waiting for more clear benefit of MIGS over alternate, more established surgical interventions. Additionally, there is a lack of clinical practice guidelines mentioning MIGS devices or procedures for ophthalmologists to refer to when choosing appropriate patients or indications, and this can contribute to the uncertainty of the placement of MIGS in the glaucoma treatment paradigm.

8. Discussion

8.1 Treatment Impact

In general, primarily in patients with mild-to-moderate OAG, there was insufficient evidence for the comparative clinical effectiveness of MIGS versus pharmacotherapy, laser therapy, different MIGS (i.e., one type of MIGS versus another), or filtration surgery. The clinical effectiveness of MIGS in combination with cataract surgery tended to be more favourable than cataract surgery alone; however, this was sometimes accompanied by greater AEs and findings were mixed. Seven different combinations of MIGS were compared with one another in nine studies,[59,60,77-81,83,86,89] but there was insufficient evidence to establish whether any particular MIGS might have comparatively greater clinical effectiveness or safety. There was insufficient evidence for the comparative clinical effectiveness and safety of MIGS in combination with cataract surgery versus filtration surgery in combination with cataract surgery. Most AEs were considered minor in all treatment groups; however, when major AEs were observed, between-group differences were uncertain due to very low-quality evidence with insufficient statistical analyses. The clinical effectiveness findings were based largely on surrogate or indirect endpoints (i.e., IOP and number of medications, both secondary outcomes), as subsequently described, and additional information on health-related QoL and patient-reported outcomes is needed. Overall, it is premature to offer specific conclusions regarding individual MIGS devices and procedures.

Evidence for the primary outcome of QoL in the Clinical Review was limited; one study[25] included a QoL outcome. In this study, the tool used to assess QoL was the NEI VFQ-25, which is considered to be more of a measure of visual function than QoL (i.e., clinically meaningful changes in QoL scores are linked to corresponding changes in VA),[195,196] and this tool did not consider the number of topical glaucoma medications that would be expected to impact QoL. The lack of evidence regarding QoL is a critical research gap because glaucoma itself and its various treatment modalities are known to have a meaningful impact on QoL.[197]

Although evidence for QoL was sparse, all studies (except for those in which pharmacotherapy was the comparator) reported information on the number of glaucoma medications as an outcome. Pharmacotherapy is associated with local or systemic side effects or toxicity,[17,18] and considerable lifetime costs,[19] and, as identified in the Patients' Perspectives and Experiences Review, is disruptive to patients in their daily life. Given the challenges of eye drops for patients with glaucoma, reduction in the number of medications is of significant value to patients and can have a substantial impact on patients' QoL. In most studies, data regarding glaucoma medications were presented in terms of the mean number of medications, and details regarding the specific medication regimens were not provided. Different medications may have varied side effects,[18] and specific medication use could differentially impact health- or vision-related QoL. Across all studies, where reported, the number of medications at pre-intervention baseline ranged from a mean of zero[58] to 3.5,[61] and the reduction in mean number of medications from pre-intervention to the longest follow-up time point ranged from approximately 0.02[74] to 3[64] medications (with one exception[25] in which the mean number of medications in the intervention group increased by approximately 0.05 over six months of follow-up). The magnitude of change in number of medications is difficult to interpret given the variability at pre-intervention baseline and follow-up and the small range in which changes can occur (i.e., there is a floor effect [zero medications] and likely a ceiling effect [e.g., a maximum number of medications that would be prescribed

before a physician would progress to different forms of treatment]). Thus, the clinical relevance — including the potential impact on QoL — of the reported reductions in medication use is unclear. It is critical that clinical outcomes include specific measures of medication burden because using eye drops is perhaps the most defining experience for patients with glaucoma.

All studies included a measure of IOP; however, IOP is considered a surrogate end point in glaucoma because it is meant to predict clinically relevant outcomes like vision loss and QoL.[198] In this regard, there is strong evidence that elevated IOP is a risk factor for the development and progression of glaucoma, and IOP is predictive of future VF loss.[10] However, many patients may develop glaucoma despite relatively low IOP, and most patients with high IOP never develop glaucoma.[198] Moreover, medications with similar effects on IOP have been shown to have dramatically different effects on VF loss, contributing to the perspective that IOP is an inappropriate surrogate end point.[198] Thus, the utility of IOP as an outcome is inherently limited. Findings were also limited in that diurnal variation was rarely[36,61,70,71,88] accounted for in the measurement of IOP. This is important because IOP is known to vary substantially throughout the day (e.g., > 10 mm Hg in an eye with glaucoma over a 24-hour period),[99] and in most studies, the overall magnitude of change in IOP from baseline to post-intervention was on a similar order of magnitude as normal diurnal fluctuations. In many cases, IOP was measured without medication washout, which likely confounded treatment effects. Notwithstanding the limitations, findings in the Clinical Review suggest that MIGS in combination with cataract surgery are at least as effective as cataract surgery alone or filtration surgery in combination with cataract surgery with respect to IOP; findings for other comparisons were unclear.

VF, a true end point, was measured directly in four studies (10%) in the Clinical Review,[34,58-60,68,89] and the results were equivocal. The paucity of information on VF may be in part because the progression of glaucoma and the impact on VF can be relatively slow, rendering assessment within the context of a clinical trial impractical and costly.[198,199] In most studies in the Clinical Review, patients were followed for at least 12 months post-intervention; however, depending on factors that impact the rate of change in VF, such as age and rate of change in IOP, this may be insufficient duration to detect clinically meaningful changes in VF.[199]

MIGS are widely cited as being expected to have a more favourable safety profile than other treatment modalities.[12,23,27,32] Information on comparative safety was limited in the current Clinical Review because the method for measuring AEs was not reported in any study. Therefore, it is uncertain whether there was any restriction on what was considered an AE, or whether information on AEs was captured systematically across patients or by convenience (e.g., only evaluated among those patients who returned for treatment to the study centre). As a result, if no detail on a particular AE was reported in a given study, it is unclear whether this was because the particular AE did not occur or whether information on that AE was not collected or reported. In addition, it was not possible to assess whether data on all patient-important AEs or harms were collected, and in many cases information was reported without statistical comparisons between groups, leading to uncertainty about the presence of between-group differences. AEs were largely considered minor in all treatment groups; however, when major AEs were observed, between-group differences were uncertain due to very low-quality evidence with insufficient statistical analyses. Given the limitations, there was insufficient evidence for the comparative safety of MIGS versus pharmacotherapy, laser therapy, different MIGS (i.e., one type of MIGS versus another), or filtration surgery. Findings for the comparative safety of MIGS in combination with cataract

surgery versus cataract surgery alone, or versus filtration surgery in combination with cataract surgery, were mixed. These results are based on very low-quality evidence and should be interpreted with caution.

In particular, although these findings generally support the safety of MIGS, in August 2018, one device, the CyPass Micro-Stent, was voluntarily withdrawn from the global market by the manufacturer due to five-year data from a long-term safety study.[37,38] In the present report, two-year follow-up data from this study were included, and at two years the CyPass Micro-Stent in combination with cataract surgery had a similar safety profile to cataract surgery alone (control group).[70] As identified in a press release,[37] at five years the group that had CyPass Micro-Stent in combination with cataract surgery had significantly greater endothelial cell loss compared with the group that had cataract surgery alone. Specifically, at five years there was an 20.4% reduction in endothelial cell density in the CyPass Micro-Stent + cataract surgery group compared with a 10.1% reduction in the control group (between-group difference: $P = 0.0032$). Similarly, "significant endothelial cell loss," defined as a reduction of greater than 30%, was more common in the CyPass Micro-Stent group (27.2%) versus the control group (10%).[38] In theory, it is possible that endothelial cell loss may be of concern with respect to the other MIGS devices and procedures, although there was no evidence for this in the studies with the longest follow-up data (i.e., three years for ECP and three or four years for iStent). The five-year findings further highlight the need for sufficient follow-up duration to detect clinically meaningful change over time.

The results of the Clinical Review impacted the approach taken in the Economic Evaluation. Substantial heterogeneity between studies that compared MIGS with pharmacotherapy, laser therapy, or filtration surgery was observed and it was considered inappropriate to conduct a network meta-analysis to pool all possible comparisons. Given these clinical findings, the economic model mirrored the comparisons that were made within the Clinical Review by conducting five pairwise comparisons of MIGS versus different treatment alternatives. The approach taken further respected the current clinical uncertainties with regards to the potential place in therapy for MIGS. MIGS have been clinically studied in broad spectrum of patients with different treatment experiences and disease severities. As such, the economic model's comparisons of MIGS with pharmacotherapy (Model 1), laser therapy (Model 2), or filtration surgery (Model 3a), and the comparison of MIGS in combination with cataract surgery versus cataract surgery alone (Model 4) reflected patients with early-stage glaucoma whereas the comparison of MIGS with or without cataract surgery versus filtration surgery with or without cataract surgery (Model 5 and 3b respectively), reflected late-stage patients with glaucoma. Although grouping all MIGS together is considered clinically inappropriate, the Clinical Review noted challenges in comparing individual MIGS devices given the limited number of studies and the considerable heterogeneity between them. As such, to provide a comprehensive understanding on the potential economic value of MIGS within each model, one MIGS device was selected for each comparison as the basis of the reference-case analysis. The specific MIGS device differed by comparison and was selected based on criteria of clinical data availability, quality of the evidence, and fitness for purpose. Extensive sensitivity analyses were conducted on the other MIGS devices, where clinical studies were identified from the Clinical Review, to inform the likely range in the cost-effectiveness of MIGS, as a class, compared with specific treatment alternatives.

Measures of the relative change in IOP and medication use between interventions from the Clinical Review were incorporated into the Economic Evaluation. Specifically, to project the lifetime progression of glaucoma, change in IOP as reported from the clinical studies was

used to estimate the change in VF. Medication use impacted the cost estimates in the model and drug adherence was considered in Model 1 that compared MIGS with pharmacotherapy. Rates of surgical complications were incorporated for all modelled surgical interventions.

The findings of the Economic Evaluation suggested that, over a lifetime (i.e., factoring subsequent treatment as disease progresses, where relevant), the cost-effectiveness of MIGS varied depending on the comparator and the patient population. Compared with pharmacotherapy, the ICUR for MIGS was $18,808 per QALY gained in patients with moderate glaucoma and, when MIGS was combined with cataract surgery compared with cataract surgery alone in patients with mild glaucoma, the ICUR was $63,626 per QALY. In patients with mild glaucoma, MIGS was dominated by laser therapy (i.e., MIGS was more costly and less effective than laser therapy). In the remaining comparisons involving filtration surgery as the comparator, filtration surgery was found to be both more costly and more effective. Specifically, the ICUR for filtration surgery ranged from $10,093 to $121,959 per QALY depending on the baseline severity of patients when compared with MIGS and, if combined with cataract surgery, the ICUR for filtration surgery with cataract surgery was $14,968 per QALY compared with MIGS with cataract surgery.

8.2 Access

One of the greatest barriers to the implementation of MIGS in Canada is the issue of access at both the system and patient level.

8.2.1 System Level

At a system level, access varies for patients living in different geographical regions, and Canada's considerable geographical size can create difficulties in caring for patients with glaucoma that live rurally or remotely. This difficulty can be because of long distances to a suitable facility, fewer specialized surgeons available for care, and problems attracting trained and experienced ophthalmologists to the area. Due to this potentially lowered access to MIGS devices and procedures and specialized ophthalmology resources, rurally or remotely located patients may be referred to receive surgical interventions much later in the glaucoma treatment pathway, and at that stage, surgeons may opt to refer patients for more invasive procedures. In the Patients' Perspectives and Experiences Review, no studies included the perspectives and experiences of persons from rural or communities. However, the Patients' Perspectives and Experiences Review team engaged with patients who described the systemic burdens of having to travel to access MIGS and follow-ups that included direct (e.g., cost of gas, hotel stays, and meals) and indirect costs to patients (e.g., time off work for caregivers).

Although these are relevant cost considerations that may impact access to MIGS, the Economic Evaluation was aligned to the decision problem with the intent of producing economic evidence that would be specifically relevant and useful to decision-makers in Canada's publicly funded health care system. As such, costs included in the analyses were specific to those paid by a public Ministry of Health and may not reflect potential indirect cost impacts from a broader societal perspective (e.g., costs borne by patients). Differential access to MIGS devices and procedures may create disparities in care across geographical locations in Canada.

The Canada Health Act does not speak to the level of care that Canadians should expect when living in rural and remote as opposed to urban areas. [158] This silence, and its

ramifications across provincial health acts, makes it difficult to judge to what degree geographical barriers to access are unjust or reasonable given the reality of a vast country with finite resources in the health care system. From an ethical perspective, geographical barriers to access raise the question of whether MIGS should be allocated preferentially to patients in rural or remote areas for the sake of promoting equity in health outcomes and burdens associated with treatment.

8.2.2 Patient Level

At a patient level, access to MIGS can vary due to the surgery itself not being an insurable benefit in the majority of provinces, necessitating the procedure or device be paid for by the facility or the patient. Unfortunately, as facilities have a restricted budget that is often shared with other specialties, this can be a barrier to implementing MIGS. Physicians have identified hospital funding models as a factor that creates challenges in allowing access for all patients, although current funding models may assist in controlling costs and managing pressure from industry. In facilities that can, or do, provide MIGS, these facilities can only fund a small fraction of the potential types of MIGS devices or procedures available for patients. Additionally, as the number of MIGS surgeries increases, the time in the OR required for these surgeries also increases, which may lengthen wait lists for patients who require the intervention.

Findings from the Patients' Perspectives and Experiences Review indicated that as patients are diagnosed through routine eye exams, those who do not get routine eye exams are at greater risk of not being diagnosed or of a delayed diagnosis. Those without health insurance and who are unable to pay out-of-pocket costs, and those who are without access to optometrists are likely at greatest risk of not having routine eye exams (including individuals located in more rural or remote settings, where there may be fewer numbers of trained optometrists or ophthalmologists). Delayed diagnoses until a more advanced condition also means that patients may no longer be considered eligible for MIGS and thus only have access to more invasive procedures.

The economic model assumed that MIGS devices and procedures would be fully covered by a Ministry of Health. However, at present, treatment with MIGS is not covered by all provinces. In such instances, patients may instead need to pay out-of-pocket for their MIGS devices. For patients who lack the financial means to pay privately for a MIGS device, or for those whose glaucoma could in principle be treated through medication but are unable to use eye drops as prescribed, the unclear status of MIGS as an "optional upgrade" versus a "medical need" may itself be a barrier to access. One specialist might consider a patient's circumstances insufficient grounds for offering that patient one of a limited supply of MIGS devices at a given facility, even though a different specialist might judge a patient in identical circumstances to clearly present medical need for MIGS treatment. Clearer guidelines on when and for whom MIGS should be considered a medical need will reduce barriers currently created by the discretionary interpretation of these concepts by professionals and health systems.

8.3 Professional Considerations

Glaucoma is a chronic condition, and as such, patient–provider relationships are central to patients' experiences of treatment. Patients appreciate professionals who support shared decision-making, and who listen and respond to their concerns. As such, providers can play an important a role in educating patients about glaucoma, and may assist patients in

confronting fears of blindness and improve their willingness to use aids and seek accommodations.

Implementation of a technology is often dependent on the diffusion of the technology into the professional community. Many physicians are “early adopters” of newer technology, including MIGS devices and procedures, although many physicians take a more cautious approach before integrating newer interventions into practice. As MIGS are relatively new technologies, this diffusion may not yet be complete. Nonetheless, new graduates of ophthalmology are frequently trained in MIGS devices and procedures, and often expect this training.

In Canada, there is a lack of appropriate formal credentialing or training standards with respect to MIGS for ophthalmologists. As MIGS have been noted to have a considerable learning curve and require technical abilities that may be challenging,[189] this lack of training standards may pose an issue for implementing MIGS in Canada.

Additionally, MIGS are not included in many ophthalmology clinical practice guidelines[168] and this lack of guidance can create difficulties for surgeons when deciding which patients are suitable candidates for MIGS, which MIGS are clinically appropriate, and which MIGS to fund in their facility. However, the role of MIGS in glaucoma management is acknowledged in the recent CGS position statement, with some potential indications outlined.[193] Despite this, there is a lack of formalized indications for the use of MIGS, leading surgeons to use their clinical discretion in selecting patients for MIGS, which may not reflect clinical need. As such, it is possible that providers’ perceptions of patients’ “compliance” may influence patient selection for MIGS. This could have the effect of rewarding “compliant” patients with access to MIGS, while those struggling with other treatment regimens are overlooked as “noncompliant.”

Moreover, it is probable that clinical discretion is influenced by the available evidence regarding effectiveness and safety, the state of which is in its infancy. Authors of the majority of studies in the Clinical Review reported several disclosures, including financial or non-financial support from industry, other involvement with industry (e.g., consulting for, or employee of, industry), or having other interests in manufacturer companies (e.g., shareholder, stock holder or patent holders). Therefore, MIGS devices and procedures with greater manufacturer support are likely to be better represented in the literature and therefore have more available evidence regarding clinical effectiveness and safety and subsequently greater uptake.

In the current landscape of MIGS use in Canada, the potential for conflicts of interest arises from incentives that institutions and professionals may have to recommend the use of specific MIGS devices to patients for reasons extraneous to patients’ individual circumstances and needs. Remedies to prevent and mitigate conflicts include transparency by surgeons and institutions in acknowledging all potential conflicts, institutional oversight in granting privileges for innovative surgeries, and candid discussion with patients.

The challenges professionals face in ensuring patients’ informed consent with respect to the potential use of MIGS begin with full candour about the clinical unknowns and uncertainties around MIGS in general and around specific MIGS devices and procedures. Beyond this, ensuring informed consent must also include assessing patients’ full understanding of the broader implications of various treatment choices in the context of patients’ individual circumstances (such as financial or geographical). These requirements make informed consent a complicated responsibility to carry out.

In order to advance more personalized selection of MIGS for patients, it will be essential for health systems, facilities, and professionals to assign and carry out the responsibility of tracking and reporting outcomes of MIGS usage.

8.4 Population Considerations

In the Clinical Review, men and women were equally represented across studies, and the majority of patients were white. This is notable because race is an important risk factor for glaucoma.[3,4,7] Similarly, none of the studies in the Patients' Perspectives and Experiences Review included the perspectives and experiences of Indigenous persons or communities. However, the issue of potential delayed diagnosis without routine eye exams may be a concern given issues with access to health care in Indigenous communities.

An important factor to consider in advancing fair access to MIGS is the demographic make-up of Canada's population with respect to racialized and ethnic groups, their distinctive risk factors for glaucoma, and the way in which societal relationships may affect their interactions with health care systems in general and glaucoma treatment in particular. Studies in the US have found that populations of African and Latino ancestry appear to have a higher risk of OAG and worse medical outcomes during the disease course.[160,161] The reasons for these differences are unknown, and how much emphasis should be put on racialized identities and genetic factors (as opposed to social, economic, and cultural ones) in understanding and countering health inequities is controversial.[163,165] Nonetheless, targeting interventions and research at racialized groups seems justifiable at present. In the US, researchers are beginning to study the use and performance of MIGS across races, ethnicities, genders, ages, and regions.[166]

While it is unknown what bearing factors identified in US populations have for racialized populations in Canada, it is highly likely that continuities and parallels do exist and must be taken into account when considering optimal MIGS use in Canada. It will be essential to gather data specific to the current and future demographic make-up of the Canadian population in order to guide decisions about optimal MIGS use. Such considerations also apply to the circumstances and needs of Canada's Indigenous populations, for whom potential genetic factors combine with common comorbidities, remote and rural residence, and histories of injustice to create distinctive needs for glaucoma prevention, treatment, and research.

Different types of glaucoma have different characteristics, and it is theoretically possible that MIGS may have greater clinical effectiveness or safety in certain types of glaucoma. All studies in the Clinical Review included primarily patients with OAG, and approximately two-thirds of the studies also included patients with different types of glaucoma (e.g., pseudoexfoliation, pigmentary, or angle-closure glaucoma). Due to the nature of the data, it was not possible to examine potential differences in treatment effects by type of glaucoma. As the Economic Evaluation reflected the patient population represented within the clinical studies, the economic findings are primarily reflective of patients with OAG. The Economic Evaluation therefore shared similar limitations as it was not possible to address whether costs-effectiveness of MIGS would differ by other types of glaucoma.

MIGS have generally been indicated for patients with mild-to-moderate glaucoma who have a lesser requirement for lowering IOP.[12,27] The Canadian Glaucoma Society's position statement also indicates MIGS for this use.[193]In the present Clinical Review, information on glaucoma severity was reported in approximately two-thirds of the included studies, and eyes with mild-to-moderate glaucoma were most commonly included although roughly one-

third of studies also included eyes with advanced or severe glaucoma. Results were presented for the complete study samples (i.e., pooled across patients with different levels of severity) and analyses by glaucoma severity were not possible. At present, the majority of the available evidence represents patients with mild-to-moderate glaucoma, with a relatively homogenous range in pre-intervention IOP, and additional work to discern differences in effectiveness by glaucoma severity is needed.

As such, the majority of the findings from the economic models reflect the potential cost-effectiveness of MIGS in patients who are receiving treatment at an early stage of glaucoma. However, as disease severity can impact costs, utilities, and options for subsequent treatment, the Economic Evaluation was stratified by baseline severity when such clinical data existed (i.e., comparison of MIGS with filtration surgery). The results from this set of comparisons highlight the fact that the cost-effectiveness of MIGS may depend on the severity of glaucoma.

Therefore, population characteristics (such as type and severity of glaucoma and community attributes) may influence the effectiveness, cost-effectiveness, access to, and experience of MIGS.

8.5 Generalizability

In the Clinical Review, seven[65,78,79,82,83,87,88] of 32 studies were conducted, at least in part, in Canada. The majority of the evidence was from developed countries, and is likely generalizable to the Canadian context. The Economic Evaluation was based on these clinical studies to inform relative treatment effects and further incorporated natural history of glaucoma from a large Canadian study.[107] Furthermore, costs and resource utilization were from Canadian sources; the findings are expected to be generalizable to the Canadian context.

The Implementation Issues Analysis was comprised of consultations with physicians practicing in Canada and also included findings from Canadian literature. However, the majority (95%) of the informants were clinicians located in urban areas, limiting the generalizability of the results to more rural or remote jurisdictions.

The findings of the Patients' Perspectives and Experiences Review included patients with glaucoma in similar health care contexts to most urban and suburban Canadian settings. The patients who the team interviewed were all based in rural areas (two in Ontario, one in Nova Scotia) and expressed similar perspectives and experiences. Taken together, this suggests the findings are largely generalizable to the Canadian context, while recognizing that individual patients have a diversity of experiences and perceptions relating to glaucoma and its treatment.

Many of the ethical and social issues around optimal MIGS use discussed in the Ethical Issues Analysis are explicitly relevant to the Canadian context in terms of barriers to equity created by Canadian health systems and by rural or remote locations. The most significant gap concerns the emerging research on glaucoma treatment and MIGS use for racialized groups in the US, given that no comparable research has yet been done in Canada. The considerations around professional conflicts of interest and responsibilities in the context of surgical innovation present no obvious concerns with respect to their validity in Canadian contexts.

8.6 Limitations

8.6.1 Evidence Gaps

Although MIGS are categorized as a particular class of interventions, each MIGS is unique in its structure and/or mechanism of action, and different MIGS may have different clinical effectiveness or safety profiles. Thus, while results in the present work are presented for "MIGS" overall, it should be recognized that these are a group of distinct interventions, and future work may identify superiority of a subset of these devices or procedures for particular patients. Differences in the use of these devices and procedures extends past the physical devices themselves, as explored in the Implementation Issues Analysis, and can also include differences in the learning curves of each device or procedure, and differences in OR time. In addition, there is some ambiguity in the field regarding what devices and procedures should rightly be classified as MIGS. In the Clinical Review, the 11 MIGS devices and procedures that were approved for use by Health Canada as of June 2018 were included; it is acknowledged that others exist (e.g., the InnFocus MicroShunt). Given the variety of available devices and procedures, it is unsurprising that there was substantial clinical heterogeneity in the available evidence. At present, there is insufficient evidence directly comparing the clinical effectiveness or safety of different MIGS, and there was no definitive evidence regarding which MIGS might be preferable, either overall or for a subset of patients.

As noted, these limitations to the Clinical Review also transferred over to the Economic Evaluation. The comparative cost-effectiveness of different MIGS devices and procedures could not be addressed. In addition, this review was conducted at a time of growing research interest in glaucoma. In particular, one area with implications to economic modelling is the natural history of glaucoma. To model the lifetime economic implications of treatment, the economic model had to incorporate the expected natural history of the condition. This was conducted by using the Hodapp-Parrish-Anderson grading scale and incorporated a Canadian randomized controlled trial that had reported VF changes over time in patients with glaucoma.[107] According to the clinical expert consulted on this review, a growing number of studies are expected in the coming years evaluating the natural history of glaucoma. As such studies become available, face validity of the model will need to be reassessed. The economic model may need to be revised to reflect new insights to natural history in modelling the long-term clinical and economic effects. However, this study only had a median follow-up duration of six years and, to model a lifetime, extrapolations were required. Given the uncertainty associated with extrapolations, sensitivity analysis was conducted with a faster disease progression and the model findings were found to be relatively robust to changes in the natural history of glaucoma.

In the Implementation Issues Analysis there was representation from Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, Yukon, and Quebec, but not all provinces or territories responded to an interview request before the deadline. Additionally, views and opinions from interviewed stakeholders may not have been fully representative of all facilities, stakeholders, or Canadian jurisdictions, but may have reflected personal experiences. There was a lack of literature regarding implementation issues in Canada specifically. Additionally, as MIGS is a quickly evolving research space, implementation issues involving MIGS may also change rapidly; some implementation issues that were described may no longer be of relevance or there may be novel issues that were not captured.

Qualitative studies on patients' experiences and perceptions of glaucoma and its treatment have focused largely on issues of effective use of medications. No included studies concerned MIGS specifically and only two studies included patients' views and experiences with surgery; thus, there are substantial limitations in what is known about patients with glaucoma with glaucoma's experiences with glaucoma surgeries including MIGS. Stakeholder feedback emphasized that these limitations are important evidence gaps and highlighted how little is known about the perspectives and experiences of patients with glaucoma about their health care and treatment more broadly. Few studies explored patients' experiences of glaucoma surgery and providers' experiences and perceptions of caring for patients with glaucoma.

Notable limitations for the Ethical Issues Analysis included the lack of published literature on ethical and social issues related to MIGS, and the lack of perspectives from specialists who thus far have decided not to use MIGS in treating patients with glaucoma.

8.6.2 Inconsistency of Results

There was substantial clinical heterogeneity in the Clinical Review. Specifically, sources of heterogeneity included differences across studies in population characteristics (e.g., type and severity of glaucoma), interventions and comparators (i.e., 24 different comparisons across the 32 included studies), outcomes (e.g., measured using different methods), time points (e.g., different follow-up duration), and study designs. As a result, it was not possible to evaluate the consistency of results.

Issue that were raised during patient engagement were not consistently identified in the literature. For example, patients raised the issue of costs associated with travel for care or for replacing eye wear; however, this concern was absent from the published literature. Inconsistency between interviews with patients and the published literature may be due to the absence of studies on glaucoma surgery and MIGS specifically.

8.6.3 Quality of Evidence

In the Clinical Review, the quality of the evidence ranged from very low to high, although the majority of the evidence was of very low or low quality. The most common concerns with the evidence were: 1) serious risk of bias that reduced the level of confidence in the observed effects, and 2) serious imprecision (e.g., only a single study for a given comparison, no measures of variability, or wide variability leading to uncertainty about the true magnitude of the effect). In addition, it was an a priori decision to describe the overall findings using the longest available follow-up time point (regardless of the end point selected by the authors) because this is most meaningful clinically; however, this may have resulted in insufficient statistical power to detect treatment effects in some cases (e.g., because studies were powered for a different outcome or time point, or no power calculation was conducted to guide appropriate enrolment, making statistical power was unclear). In contrast, in some studies the investigators carried out a multiplicity of analyses without an adequate statistical plan, which may have resulted in the detection of spurious associations. Given the heterogeneity in comparisons, few meta-analyses were possible, and those that were conducted were of limited utility (e.g., because it was only possible to pool absolute values at follow-up, rather than pooling change from baseline). Evidence for the primary outcome of interest was extremely limited (i.e., QoL was only examined in a single study), and conclusions were based on secondary outcomes.

Included studies in the Patients' Perspectives and Experiences Review were assessed overall as being of low quality, frequently due to methods that collected thin data or reported superficial or non-robust findings. Most studies poorly reported participant characteristics, including age, disease severity, and time since diagnosis. The impact of poor quality studies prohibited the ability to isolate and describe the experiences of those with early or moderate glaucoma who would be eligible for MIGS.

For feasibility reasons only studies published in English or French were eligible for inclusion in both the Clinical Review and the Patients' Perspectives and Experiences Review. It is acknowledged that there is a potential for language bias when language restrictions are used; however, there is also evidence for minimal impact of including studies published in other languages.

8.6.4 Assumptions

Several assumptions were required in order to construct the economic model. For instance, the natural history of glaucoma had to be modelled over a lifetime time horizon. Health states in the economic model were defined according to the Hodapp-Parrish-Anderson grading scale and, as research continues to evolve in the area of VF staging and disease progression, the conceptualization of the economic model may need to be revisited. Within the clinical studies, treatment effects were most commonly described as a change in IOP and the economic model had to utilize a predictive equation to describe the relationship between a clinical change in IOP and its impact on VF. Confirmatory research remains necessary to evaluate the predictive ability of this equation that was used in the economic model. Where possible, sensitivity analyses were conducted to address the potential impact of these assumptions on the economic findings. For the most part, the model was found to be robust to these assumptions as sensitivity analyses found that the model was most sensitive to parameters pertaining to the relative effectiveness of treatments and the costs associated with MIGS.

In the Patients' Perspectives and Experiences Review it became apparent that normative ideals surrounding patient compliance acted as a starting point for many of the included studies. By focusing lines of questioning on what constitutes "barriers" or "facilitators" to patient compliance, these studies embrace an assumption that physicians' treatment goals of lowering IOP are reflective of patients' treatment goals. As noted in the review, this assumption tends to miss the mark as increases in IOP largely go unnoticed by patients whose treatment goals pivot around concerns with improved clinical interactions, decreased medication burdens, and eventual sight loss. This assumption created a slippage that prevented the review from seriously engaging with the challenges of existing pharmacotherapies for glaucoma as a way of identifying or examining the potential benefits or detriments of MIGS for patients.

8.7 Directions for Future Research

In order to facilitate decisions around appropriate patient selection, detailed reporting of patient characteristics, including treatment history, and type and severity of glaucoma, is required. Long-term follow-up and measurement of direct, patient-important end points (e.g., VF, QoL, and AEs) will provide greater insight regarding the comparative clinical effectiveness and safety of MIGS over time, and will enable a more targeted Economic Evaluation. In general, comparative evidence from head-to-head study designs is needed. Furthermore, as the economic model was sensitive to the costs of MIGS, detailed micro-

costing of MIGS procedures may allow for greater certainty in the true absolute and incremental costs of MIGS to better inform the potential economic value of MIGS.

Implementation analyses would benefit from future research into aspects of the CICI INTEGRATE-HTA framework[177] that were not present in the literature, including setting, geographical area, epidemiology, socioeconomic and sociocultural aspects, politics, and legal aspects. Implementation research regarding MIGS may also benefit from branching out into surveys involving more general ophthalmologists and cataract surgeons, to gain their perspective on MIGS use in Canada, as they may be able to perform MIGS surgeries in addition to surgical ophthalmologists.

There is a need for well-designed qualitative studies that focus on the patients' and providers' perceptions and experiences with MIGS before and after surgery. Additionally, further qualitative research in patients with glaucoma would benefit from improved reporting of participants' disease severity and time since diagnosis and attention to the way these factors influence patients' perspectives and experiences.

Two important areas for further research relevant to the ethical and social concerns are: 1) knowledge of how glaucoma treatment in general and MIGS treatment options in particular intersect with racialized groups within Canada's demographic make-up; and 2) whether and how specialists can reasonably incorporate patients' circumstantial details (e.g., financial means, geographical constraints) into informed-consent discussions around potential choice of MIGS as a glaucoma treatment.

MIGS devices and procedures are relatively new, and research regarding MIGS is still in its infancy. Indeed, the number of publications concerning MIGS has increased steadily over the past decade (Figure 1), and there are several registered clinical trials underway along with additional follow-up from existing clinical trials. During the preparation of this report an additional relevant study was published,[200] an in-press study was submitted by a manufacturer[201] (both largely consistent with other findings), and an additional MIGS device was approved for use in Canada (the Hydrus Microstent). As manufacturers and clinicians continue to innovate, the ongoing development and refinement of MIGS is anticipated. As additional research into the clinical effectiveness and safety, cost-effectiveness, patients' perspectives and experiences, ethical issues, and implementation issues of MIGS devices and procedures for adult patients with glaucoma emerges, reassessment will be needed.

9. Conclusions

Overall, the findings from the Clinical Review suggested that, primarily in patients with mild-to-moderate OAG, there was insufficient evidence for the comparative clinical effectiveness and safety of MIGS versus pharmacotherapy, laser therapy, different MIGS (i.e., one type of MIGS versus another), or filtration surgery. The clinical effectiveness of MIGS in combination with cataract surgery tended to be more favourable than cataract surgery alone; however, findings for comparative safety were mixed. There was insufficient evidence for the comparative clinical effectiveness and safety of MIGS in combination with cataract surgery versus filtration surgery in combination with cataract surgery. These conclusions were based largely on indirect outcomes (i.e., IOP and number of medications as surrogates for VF and QoL, respectively); particularly in the context of such inconclusive clinical outcomes, increased attention to patient-important outcomes (e.g., health-related QoL) is imperative. This evidence should be interpreted with caution, given that, although MIGS are categorized as a particular class of interventions, each is unique in terms of its structure and mechanism of action, and may reasonably be anticipated to have different clinical effectiveness and safety profiles. There was insufficient evidence to offer specific conclusions regarding individual MIGS devices and procedures, and there was no definitive evidence regarding which MIGS might be preferable, either overall or for a subset of patients.

Definitive conclusions on the attractiveness of MIGS from a cost-effectiveness perspective to inform its potential place in therapy are precluded given the uncertainty in the analysis and the heterogeneity in the clinical data. The Economic Evaluation provided some early signals to scenarios where MIGS may be economically attractive. By incorporating the available Clinical Review findings on relative efficacy and safety of MIGS, the Economic Evaluation found that the lifetime cost-effectiveness of MIGS differed according to the treatment modality being compared and the baseline disease severity. Specifically, MIGS seemed to offer more clinical benefit at a higher cost when compared with pharmacotherapy or when performed in combination with cataract surgery instead of cataract surgery alone. Results were sensitive to costs associated with MIGS and the purported long-term benefits of MIGS. These findings highlight the fact that specific situations may exist whereby MIGS may be cost-effective but, if used indiscriminately, MIGS may not always be the most cost-effective treatment option for certain patients.

Current treatments for glaucoma in the form of eye drops were highly disruptive for patients who welcomed the opportunity to reduce or eliminate the need to take eye drops. Patients' perceptions and experiences of glaucoma were highly shaped by the societal understandings and awareness of glaucoma and of blindness. While treatments may reduce IOP and slow the progression of their glaucoma, once diagnosed, patients moved through the world with glaucoma. Experiencing glaucoma as a chronic condition, patient–provider relationships were central to patients' experiences with glaucoma treatment and provided an opportunity to assist patients to become acquainted with glaucoma, improve adherence, and adjust to vision changes.

Implementation of MIGS in Canada is a multi-factorial issue, including factors such as funding models, organization, and professional considerations. Currently, access is limited for many Canadians because of geography or setting, restricted supply of the technology, or slow uptake of the technology by providers.

Ethically and socially relevant issues include the need for guidelines to help institutions and surgeons fairly allocate MIGS under conditions of scarcity; concerns about public coverage

versus private payment for MIGS, as well as diverging views of MIGS as an “optional upgrade” or a medical need; and concerns about equitable access to MIGS for patients living in rural and remote locations and for patients from certain racialized groups. Ethical concerns related to the context of surgical innovation include conflicts of interest; assignment of responsibility for tracking and reporting outcomes of MIGS usage; and challenges defining and carrying out surgeons’ responsibility to enable informed patient consent with respect to the potential use of MIGS.

This is a rapidly changing field and as substantial new evidence regarding the clinical effectiveness and safety, cost-effectiveness, patients’ perspectives and experiences, ethical issues, and implementation issues of MIGS devices and procedures emerges, reassessment will be needed.

References

1. Zhang ML, Hirunyachote P, Jampel H. Combined surgery versus cataract surgery alone for eyes with cataract and glaucoma. *Cochrane Database Syst Revs.* 2015;7:CD008671.
2. Boland MV, Ervin AM, Friedman D, Jampel H, Hawkins B. Treatment for glaucoma: comparative effectiveness. *Comparative effectiveness review no.60.* Rockville (MD): Agency for Healthcare Research and Quality; 2012: https://www.ncbi.nlm.nih.gov/books/NBK95391/. Accessed 2017 Dec 22.
3. Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert Committee, Canadian Ophthalmological Society. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of glaucoma in the adult eye. *Can J Ophthalmol.* 2009;44 Suppl 1:S7-93.
4. Hazin R, Hendrick AM, Kahook MY. Primary open-angle glaucoma: diagnostic approaches and management. *J Natl Med Assoc.* 2009;101(1):46-50.
5. Iskedjian M, Walker J, Vicente C, Trope GE, Buys Y, Einarson TR, et al. Cost of glaucoma in Canada: Analyses based on visual field and physician's assessment. *J Glaucoma.* 2003;12(6):456-462.
6. The National Coalition for Vision Health. Vision loss in Canada 2011. Ottawa (ON): Canadian Ophthalmological Society; 2011: http://www.cos-sco.ca/wp-content/uploads/2012/09/VisionLossinCanada_e.pdf. Accessed 2017 Aug 18.
7. Harasymowycz P, Birt C, Gooi P, Heckler L, Hutnik C, Jinapriya D, et al. Medical management of glaucoma in the 21st century from a Canadian perspective. *J Ophthalmol.* 2016:6509809.
8. *Glaucoma: guide.* Ottawa (ON): Ottawa Hospital; 2008.
9. Glaucoma: facts & figures. Clarksburg (MD): BrightFocus© Foundation; 2017: http://www.brightfocus.org/glaucoma/article/glaucoma-facts-figures. Accessed 2016 Apr 17.
10. Miglior S, Bertuzzi F. Relationship between intraocular pressure and glaucoma onset and progression. *Curr Opin Pharmacol.* 2013;13(1):32-35.
11. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol.* 2006;90(3):262-267.
12. Richter GM, Coleman AL. Minimally invasive glaucoma surgery: current status and future prospects. *Clinical Ophthalmology.* 2016;10:189-206.
13. Conlon R, Saheb H, Ahmed II. Glaucoma treatment trends: a review. *Canadian Journal of Ophthalmology.* 2017;52(1):114-124.
14. Roberts SJ, Mulvahill M, SooHoo JR, Pantcheva MB, Kahook MY, Seibold LK. Efficacy of combined cataract extraction and endoscopic cyclophotocoagulation for the reduction of intraocular pressure and medication burden. *Int J Ophthalmol.* 2016;9(5):693-698. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4886875. Accessed 2017 Aug 4.
15. Okeke CO, Quigley HA, Jampel HD, Ying GS, Plyler RJ, Jiang Y, et al. Adherence with topical glaucoma medication monitored electronically the Travatan Dosing Aid study. *Ophthalmology.* 2009;116(2):191-199.
16. Terminology and guidelines for glaucoma. 4th ed ed. Savona (ITA): European Glaucoma Society; 2014: http://www.icoph.org/dynamic/attachments/resources/egs_guidelines_4_english.pdf. Accessed 2017 Aug 8.
17. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med.* 1990;112(2):120-125.
18. Sambhara D, Aref AA. Glaucoma management: relative value and place in therapy of available drug treatments. *Ther Adv Chronic Dis.* 2014;5(1):30-43.
19. Iordanous Y, Kent JS, Hutnik CM, Malvankar-Mehta MS. Projected cost comparison of Trabectome, iStent, and endoscopic cyclophotocoagulation versus glaucoma medication in the Ontario Health Insurance Plan. *J Glaucoma.* 2014;23(2):e112-e118.
20. Coleman AL, Lum FC, Velentgas P, Su Z, Gliklich RE, RiGOR Study Group. Impact of treatment strategies for open angle glaucoma on intraocular pressure: the RiGOR study. *J Comp Eff Res.* 2016;5(1):87-98.
21. Leahy KE, White AJ. Selective laser trabeculoplasty: current perspectives. *Clin Ophthalmol.* 2015;9:833-841.
22. Bovee CE, Pasquale LR. Evolving surgical interventions in the treatment of glaucoma. *Semin Ophthalmol.* 2017;32(1):91-95.
23. Saheb H, Ahmed II. Micro-invasive glaucoma surgery: current perspectives and future directions. *Curr Opin Ophthalmol.* 2012;23(2):96-104.
24. Edmunds B, Thompson JR, Salmon JF, Wormald RP. The National Survey of Trabeculectomy. III. Early and late complications. *Eye (Lond).* 2002;16(3):297-303.
25. Pahlitzsch M, Klamann MK, Pahlitzsch ML, Gonnermann J, Torun N, Bertelmann E. Is there a change in the quality of life comparing the micro-invasive glaucoma surgery (MIGS) and the filtration technique trabeculectomy in glaucoma patients? *Graefes Arch Clin Exp Ophthalmol.* 2017;255(2):351-357.
26. Hoeh H, Vold SD, Ahmed IK, Anton A, Rau M, Singh K, et al. Initial clinical experience with the CyPass Micro-Stent: Safety and surgical outcomes of a novel supraciliary microstent. *J Glaucoma.* 2016;25(1):106-112.
27. Brandao LM, Grieshaber MC. Update on Minimally Invasive Glaucoma Surgery (MIGS) and new implants. *J Ophthalmol.* 2013;2013:705915.
28. Kaplowitz K, Bussel II, Honkanen R, Schuman JS, Loewen NA. Review and meta-analysis of ab-interno trabeculectomy outcomes. *Br J Ophthalmol.* 2016;100(5):594-600.

29. SooHoo JR, Seibold LK, Radcliffe NM, Kahook MY. Minimally invasive glaucoma surgery: current implants and future innovations. *Can J Ophthalmol.* 2014;49(6):528-533.

30. Malvankar-Mehta MS, Chen YN, Iordanous Y, Wang WW, Costella J, Hutnik CM. iStent as a solo procedure for glaucoma patients: A systematic review and meta-analysis. *PLoS One.* 2015;10(5):e0128146.

31. Ahmed II. MIGS and the FDA: What's in a name? *Ophthalmology.* 2015;122(9):1737-1739.

32. Caprioli J, Kim JH, Friedman DS, Kiang T, Moster MR, Parrish RK, et al. Special commentary: Supporting innovation for safe and effective minimally invasive glaucoma surgery: Summary of a joint meeting of the American Glaucoma Society and the Food and Drug Administration, Washington, DC, February 26, 2014. *Ophthalmology.* 2015;122(9):1795-1801.

33. Malvankar-Mehta MS, Iordanous Y, Chen YN, Wang WW, Patel SS, Costella J, et al. iStent with phacoemulsification versus phacoemulsification alone for patients with glaucoma and cataract: A meta-analysis. *PLoS One.* 2015;10(7):e0131770.

34. Samuelson TW, Katz LJ, Wells JM, Duh YJ, Giamporcaro JE, US iStent Study Group. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. *Ophthalmology.* 2011;118(3):459-467.

35. Grover DS, Godfrey DG, Smith O, Feuer WJ, Montes de Oca I, Fellman RL. Gonioscopy-assisted transluminal trabeculotomy, ab interno trabeculotomy: Technique report and preliminary results. *Ophthalmology.* 2014;121(4):855-861.

36. Fea AM, Belda JI, Rekas M, Junemann A, Chang L, Pablo L, et al. Prospective unmasked randomized evaluation of the iStent inject® versus two ocular hypotensive agents in patients with primary open-angle glaucoma. *Clin Ophthalmol.* 2014;8:875-882.

37. Alcon announces voluntary global market withdrawal of CyPass Micro-Stent for surgical glaucoma. Fort Worth (TX): Novartis AG; 2018: https://www.alcon.com/news/media-releases/alcon-announces-voluntary-global-market-withdrawal-cypass-micro-stent-surgical. Accessed 2018 Sep 10.

38. Durr GM, Ahmed I. Endothelial cell loss and MIGS: What we know and don't know. *Glaucoma Today* 2018; http://glaucomatoday.com/2018/10/endothelial-cell-loss-and-migs-what-we-know-and-dont-know/. Accessed October 29, 2018.

39. New treatment improves vision health for Canadians with glaucoma. *Personal Health News* 2017; http://www.personalhealthnews.ca/research-and-innovations/new-treatment-improves-vision-health-for-canadians-with-glaucoma. Accessed 2017 Sep 28.

40. Optimal use of Minimally Invasive Glaucoma Surgery: A Health Technology Assessment — Project protocol. PROSPERO Registration Number: CRD42018082223. *CADTH Optimal use report; vol,.8, no.1a*. Ottawa (ON): CADTH; 2018: https://cadth.ca/sites/default/files/pdf/OP0532_MIGS_Protocol.pdf. Accessed 2018 Jun 7.

41. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol.* 2011;64(4):395-400.

42. Dekkers OM, Egger M, Altman DG, Vandenbroucke JP. Distinguishing case series from cohort studies. *Ann Intern Med.* 2012;156(1 Pt 1):37-40.

43. *Distiller SR* [computer program]. Ottawa (ON): Evidence Partners; 2017.

44. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions.* Version 5.1.0 ed. London (England): The Cochrane Collaboration; 2011.

45. Sterne JAC, Hernán MA, Reeves BC, Savoi J, Berkman ND, Viswanathan M, et al. The ROBINS-1 tool (risk of bias in non-randomized studies - of interventions). *BMJ.* 2016;355:i4919.

46. Guyatt GH, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64(4):383-394.

47. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, onso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol.* 2011;64(4):407-415.

48. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *J Clin Epidemiol.* 2011;64(12):1294-1302.

49. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol.* 2011;64(12):1303-1310.

50. Guyatt GH, Oxman AD, Kunz R, Brozek J, onso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol.* 2011;64(12):1283-1293.

51. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin Epidemiol.* 2011;64(12):1277-1282.

52. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol.* 2011;64(12):1311-1316.

53. Devereaux PJ, Choi PT, El-Dika S, Bhandari M, Montori VM, Schunemann HJ, et al. An observational study found that authors of randomized controlled trials frequently use concealment of randomization and blinding, despite the failure to report these methods. *J Clin Epidemiol.* 2004;57(12):1232-1236.

54. Schunemann H, Brozek J, Guyatt G, Oxman A, editors. *GRADE handbook.* 2013.

55. What is GRADE? *BMJ Best Practice*. London (GB): BMJ Publishing Group Limited; 2017: https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/. Accessed 2018 Sep 12.

56. Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. *J Clin Epidemiol.* 2013;66(2):173-183.

57. Valentine JC. How many studies do you need? A primer on statistical power for meta-analysis. *JEBS.* 2010;35(2):215-247.

58. Vold SD, Voskanyan L, Tetz M, Auffarth G, Masood I, Au L, et al. Newly diagnosed primary open-angle glaucoma randomized to 2 trabecular bypass stents or prostaglandin: Outcomes through 36 months. *Ophthalmol Ther.* 2016;5(2):161-172.

59. Katz LJ, Erb C, Carceller GA, Fea AM, Voskanyan L, Giamporcaro JE, 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;12:255-262.

60. Katz LJ, Erb C, Carceller GA, Fea AM, Voskanyan L, Wells JM, et al. Prospective, randomized study of one, two, or three trabecular bypass stents in open-angle glaucoma subjects on topical hypotensive medication. *Clin Ophthalmol.* 2015;9:2313-2320.

61. Lima FE, Magacho L, Carvalho DM, Susanna R, Avila MP. A prospective, comparative study between endoscopic cyclophotocoagulation and the Ahmed drainage implant in refractory glaucoma. *J Glaucoma.* 2004;13(3):233-237.

62. Fea AM, Ahmed II, Lavia C, Mittica P, Consolandi G, Motolese I, et al. Hydrus microstent compared to selective laser trabeculoplasty in primary open angle glaucoma: one year results. *Clin Exp Ophthalmol.* 2017;45(2):120-127.

63. Murakami Y, Akil H, Chahal J, Dustin L, Tan J, Chopra V, et al. Endoscopic cyclophotocoagulation versus second glaucoma drainage device after prior aqueous tube shunt surgery. *Clin Exp Ophthalmol.* 2017;45(3):241-246.

64. Jea SY, Francis BA, Vakili G, Filippopoulos T, Rhee DJ. Ab interno trabeculectomy versus trabeculectomy for open-angle glaucoma. *Ophthalmology.* 2012;119(1):36-42.

65. Schlenker MB, Gulamhusein H, Conrad-Hengerer I, Somers A, Lenzhofer M, Stalmans I, et al. Efficacy, safety, and risk factors for failure of standalone ab interno gelatin microstent implantation versus standalone trabeculectomy. *Ophthalmology.* 2017;124(11):1579-1588.

66. Fea AM, Consolandi G, Zola M, Pignata G, Cannizzo P, Lavia C, et al. Micro-bypass implantation for primary open-angle glaucoma combined with phacoemulsification: 4-year follow-up. *J Ophthalmol.* 2015;2015:795357.

67. Fea AM. Phacoemulsification versus phacoemulsification with micro-bypass stent implantation in primary open-angle glaucoma: randomized double-masked clinical trial. *J Cataract Refract Surg.* 2010;36(3):407-412.

68. Craven ER, Katz LJ, Wells JM, Giamporcaro JE, iStent Study Group. Cataract surgery with trabecular micro-bypass stent implantation in patients with mild-to-moderate open-angle glaucoma and cataract: two-year follow-up. *J Cataract Refract Surg.* 2012;38(8):1339-1345.

69. Fernandez-Barrientos Y, Garcia-Feijoo J, JM M-d-l-C, Pablo LE, Fernandez-Perez C, Garcia SJ. Fluorophotometric study of the effect of the glaukos trabecular microbypass stent on aqueous humor dynamics. *Invest Ophthalmol Vis Sci.* 2010;51(7):3327-3332.

70. Vold S, Ahmed II, Craven ER, Mattox C, Stamper R, Packer M, et al. Two-year COMPASS trial results: Supraciliary microstenting with phacoemulsification in patients with open-angle glaucoma and cataracts. *Ophthalmology.* 2016;123(10):2103-2112.

71. Pfeiffer N, Garcia-Feijoo J, Martinez-de-la-Casa JM, Larrosa JM, Fea A, Lemij H, et al. A randomized trial of a Schlemm's canal microstent with phacoemulsification for reducing intraocular pressure in open-angle glaucoma. *Ophthalmology.* 2015;122(7):1283-1293.

72. Kang S, Luk S, Han H, Cordeiro MF, Ahmed F, Bloom P, et al. Refractive outcome of combined phacoemulsification and endoscopic cyclophotocoagulation. *International Ophthalmology.* 2017;37(6):1311-1317.

73. Perez Bartolome F, Rodrigues IA, Goyal S, Block E, Lim S, Alaghband P, et al. Phacoemulsification plus endoscopic cyclophotocoagulation versus phacoemulsification alone in primary open-angle glaucoma. *Eur J Ophthalmol.* 2017:0.

74. Sheybani A, Saboori M, Kim JM, Gammon H, Lee AY, Bhorade AM. Effect of endoscopic cyclophotocoagulation on refractive outcomes when combined with cataract surgery. *Can J Ophthalmol.* 2015;50(3):197-201.

75. Siegel MJ, Boling WS, Faridi OS, Gupta CK, Kim C, Boling RC, et al. Combined endoscopic cyclophotocoagulation and phacoemulsification versus phacoemulsification alone in the treatment of mild to moderate glaucoma. *Clin Exp Ophthalmol.* 2015;43(6):531-539.

76. El Wardani M, Bergin C, Achache F, Sharkawi E. Evaluating the trabecular micro-bypass stent combined with phacoemulsification compared to phacoemulsification alone. *Klin Monbl Augenheilkd.* 2015;232(4):442-445.

77. Gonnermann J, Bertelmann E, Pahlitzsch M, Maier-Wenzel AB, Torun N, Klamann MK. Contralateral eye comparison study in MICS & MIGS: Trabectome(R) vs. iStent inject(R). *Graefes Arch Clin Exp Ophthalmol.* 2017;255(2):359-365.

78. Khan M, Saheb H, Neelakantan A, Fellman R, Vest Z, Harasymowycz P, et al. Efficacy and safety of combined cataract surgery with 2 trabecular microbypass stents versus ab interno trabeculotomy. *J Cataract Refract Surg.* 2015;41(8):1716-1724.

79. Kurji K, Rudnisky CJ, Rayat JS, Arora S, Sandhu S, Damji KF, et al. Phaco-trabectome versus phaco-iStent in patients with open-angle glaucoma. *Can J Ophthalmol.* 2017;52(1):99-106.

80. Vlasov A, Kim WI. The efficacy of two trabecular bypass stents compared to one in the management of open-angle glaucoma. *Mil Med.* 2017;182(S1):222-225.

81. Ferguson TJ, Swan R, Sudhagoni R, Berdahl JP. Microbypass stent implantation with cataract extraction and endocyclophotocoagulation versus microbypass stent with cataract extraction for glaucoma. *J Cataract Refract Surg.* 2017;43(3):377-382.

82. Marco S, Damji KF, Nazarali S, Rudnisky CJ. Cataract and Glaucoma Surgery: Endoscopic Cyclophotocoagulation versus Trabeculectomy. *Middle East Afr J Ophthalmol.* 2017;24(4):177-182.

83. Belovay GW, Naqi A, Chan BJ, Rateb M, Ahmed II. Using multiple trabecular micro-bypass stents in cataract patients to treat open-angle glaucoma. *Journal of Cataract and Refractive Surgery.* 2012;38(11):1911-1917.

84. Francis BA, Berke SJ, Dustin L, Noecker R. Endoscopic cyclophotocoagulation combined with phacoemulsification versus phacoemulsification alone in medically controlled glaucoma. *J Cataract Refract Surg.* 2014;40(8):1313-1321.

85. Kinoshita-Nakano E, Nakanishi H, Ohashi-Ikeda H, Morooka S, Akagi T. Comparative outcomes of trabeculotomy ab externo versus trabecular ablation ab interno for open angle glaucoma. *Jpn J Ophthalmol.* 2018:1-8.

86. Dorairaj SK, Kahook MY, Williamson BK, Seibold LK, El Mallah MK, Singh IP. A multicenter retrospective comparison of goniotomy versus trabecular bypass device implantation in glaucoma patients undergoing cataract extraction. *Clin Ophthalmol.* 2018;12:791-797.

87. Ting JLM, Rudnisky CJ, Damji KF. Prospective randomized controlled trial of phaco-trabectome versus phaco-trabeculectomy in patients with open angle glaucoma. *Can J Ophthalmol.* 2018.

88. Samuelson TW, Chang DF, Marquis R, Flowers B, Lim KS, Ahmed IIK, et al. A Schlemm Canal Microstent for Intraocular Pressure Reduction in Primary Open-Angle Glaucoma and Cataract: The HORIZON Study. *Ophthalmology.* 2018.

89. Moghimi S, Hamzeh N, Mohammadi M, Khatibi N, Bowd C, Weinreb RN. Combined glaucoma and cataract surgery: comparison of viscocanalostomy, endocyclophotocoagulation, and ab interno trabeculectomy. *J Cataract Refract Surg.* 2018;44(5):557-565.

90. Akil H, Huang P, Chopra V, Francis B. Assessment of Anterior Segment Measurements with Swept Source Optical Coherence Tomography before and after Ab Interno Trabeculotomy (Trabectome) Surgery. *J Ophthalmol.* 2016;2016:4861837.

91. Fea AM, Spinetta R, Cannizzo PML, Consolandi G, Lavia C, Aragno V, et al. Evaluation of Bleb Morphology and Reduction in IOP and Glaucoma Medication following Implantation of a Novel Gel Stent. *J Ophthalmol.* 2017;2017:9364910.

92. Mills RP, Budenz DL, Lee PP, Noecker RJ, Walt JG, Siegartel LR, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. *Am J Ophthalmol.* 2006;141(1):24-30.

93. Zeyen T, Roche M, Brigatti L, Caprioli J. Formulas for conversion between Octopus and Humphrey threshold values and indices. *Graefes Arch Clin Exp Ophthalmol.* 1995;233(10):627-634.

94. Krefting L. Rigor in qualitative research: the assessment of trustworthiness. *Am J Occup Ther.* 1991;45(3):214-222.

95. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol.* 2001;119(7):1050-1058.

96. Elliott DB. The good (logMAR), the bad (Snellen) and the ugly (BCVA, number of letters read) of visual acuity measurement. *Ophthalmic Physiol Opt.* 2016;36(4):355-358.

97. Lee JW, Yick DW, Tsang S, Yuen CY, Lai JS. Efficacy and Safety of Trabectome Surgery in Chinese Open-Angle Glaucoma. *Medicine.* 2016;95(15):e3212.

98. Parikh R, O'Keefe L, Salowe R, Mccoskey M, Pan W, Sankar P, et al. Factors associated with participation by African Americans in a study of the genetics of glaucoma. *Ethn Health.* 2017:1-11.

99. Agnifili L, Mastropasqua R, Frezzotti P, Fasanella V, Motolese I, Pedrotti E, et al. Circadian intraocular pressure patterns in healthy subjects, primary open angle and normal tension glaucoma patients with a contact lens sensor. *Acta Ophthalmol.* 2015;93(1):e14-e21.

100. Guedes RA, Guedes VM, Chaoubah A. Cost-effectiveness comparison between non-penetrating deep sclerectomy and maximum-tolerated medical therapy for glaucoma within the Brazilian National Health System (SUS). *Arq Bras Oftalmol.* 2012;75(1):11-15.

101. Chan PP, Li EY, Tsoi KKF, Kwong YY, Tham CC. Cost-effectiveness of Phacoemulsification Versus Combined Phacotrabeculectomy for Treating Primary Angle Closure Glaucoma. *J Glaucoma.* 2017;26(10):911-922.

102. van Gestel A, Schouten JS, Beckers HJ, Severens JL, Hendrikse F, Webers CA. The long term effectiveness and cost-effectiveness of initiating treatment for ocular hypertension. *Acta Ophthalmol.* 2014;92(6):513-523.

103. El-Khamery AA, Mohamed AI, Swify HE, Mohammed AI. Cost-effectiveness of glaucoma management with monotherapy medications in Egypt. *J Adv Pharm Technol Res.* 2017;8(7):25-28.

104. Tan SZ, Au L. Manchester iStent study: 3-year results and cost analysis. *Eye (Lond).* 2016;30(10):1365-1370.

105. Guidelines for the economic evaluation of health technologies:Canada. 4th edition ed. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Accessed 2018 Jul 28.

106. Hodapp E, Parrish RKI, Anderson DR. Glaucoma grading scale (Hodapp-Parrish-Anderson). *Clinical decisions in glaucoma*. St Louis (MI): The CV Mosby Co.; 1993.

107. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol.* 2002;120(10):1268-1279.

108. Life Tables, Canada, provinces and territories 1980/1982 to 2014/2016. Ottawa (ON): Statistics Canada; 2018: https://www150.statcan.gc.ca/n1/pub/84-537-x/84-537-x2018002-eng.htm. Accessed 2018 Jul 12.

109. Chauhan BC, Mikelberg FS, Artes PH, Balazsi AG, LeBlanc RP, Lesk MR, et al. Canadian Glaucoma Study: 3. Impact of risk factors and intraocularpressure reduction on the rates of visual field change. *Arch Ophthalmol.* 2010;128(10):1249.

110. Kaplan RI, De Moraes CG, Cioffi GA, Al-Aswad LA, Blumberg DM. Comparative Cost-effectiveness of the Baerveldt Implant, Trabeculectomy With Mitomycin, and Medical Treatment. *JAMA Ophthalmol.* 2015;133(5):560-567.

111. Newman-Casey PA, Robin AL, Blachley T, Farris K, Heisler M, Resnicow K, et al. The Most Common Barriers to Glaucoma Medication Adherence: A Cross-Sectional Survey. *Ophthalmology.* 2015;122(7):1308-1316.

112. Djafari F, Lesk MR, Giguere CE, Siam G, Freeman EE. Impact of a Brief Educational Intervention on Glaucoma Persistence: A Randomized Controlled Clinical Trial. *Ophthalmic Epidemiol.* 2015;22(6):380-386.

113. van Gestel A. *Glaucoma management : economic evaluations based on a patient level simulation model.* Maastricht (NLD): Maastrict University; 2012.

114. Consumer Price Index, monthly, not seasonally adjusted. Ottawa (ON): Statistics Canada; 2018: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000401. Accessed 2018 Jul 12.

115. Ontario drug benefit formulary/comparative drug index. Toronto (ON): Ontario Ministry of Health and Long-Term Care; 2018: https://www.healthinfo.moh.gov.on.ca/formulary/. Accessed 2018 Jul 12.

116. Interactive drug benefit list (iDBL). Edmonton (AB): Alberta Health; 2018: https://www.ab.bluecross.ca/dbl/publications.html#dbl. Accessed 2018 Jun 12.

117. Ontario Ministry of Health and Long Term Care OCCI costing analysis tool. *Health Data Branch Web Portal*. Toronto (ON): Ministry of Health and Long Term Care; 2015: https://hsim.health.gov.on.ca/hdbportal/.

118. Interactive health data application. Edmonton (AB): Government of Alberta; 2018: http://www.ahw.gov.ab.ca/IHDA_Retrieval/. Accessed 2018 Jun 12.

119. Macario A, Vitez TS, Dunn B, McDonald T. Where are the costs in perioperative care? Analysis of hospital costs and charges for inpatient surgical care. *Anesthesiology.* 1995;83(6):1138-1144.

120. Schedule of benefits: Physician Services Under the Health Insurance Act (October 30, 2015 (Effective December 21, 2015)). Toronto (ON): Ontario Ministry of Health and Long Term Care; 2015: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20151221.pdf. Accessed 2018 Jun 12.

121. Lee PP, Walt JG, Doyle JJ, Kotak SV, Evans SJ, Budenz DL, et al. A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. *Arch Ophthalmol.* 2006;124(1):12-19.

122. Ambutech C-Grip Support Cane 40in. *Shop cnib*. Toronto (ON): CNIB; 2018: http://shop.cnib.ca/ProductDetail/can4121229540.

123. Esch 1624-11 MaxTV 2.1X Telescopic Glasses. *Shop cnib*. Toronto (ON): CNIB; 2018: http://shop.cnib.ca/ProductDetail/mag1200210003. Accessed 2018 Jul 27.

124. Understand your glaucoma diagnosis. San Francisco (CA): Glaucoma Research Foundation; 2018: https://www.glaucoma.org/treatment/understand-your-glaucoma-diagnosis.php. Accessed 2018 Jul 27.

125. Alberta Health Insurance Plan: medical price list as of 01 April 2017. Edmonton (AB): Government of Alberta; 2017: https://open.alberta.ca/dataset/376dc12c-5bbb-494e-810b-ad3a6e13874a/resource/f4017e43-3407-4551-8ac7-8c60065617e4/download/SOMB-Medical-Prices-2017-04.pdf. Accessed 2018 Jul 12.

126. Kerr NM, Wang J, Barton K. Minimally invasive glaucoma surgery as primary stand-alone surgery for glaucoma. *Clin Exp Ophthalmol.* 2017;45(4):393-400.

127. Booth A, Noyes J, Flemming K, Gerhardus A, Wahlster P, van der Wilt GJ, et al. *Guidance on choosing qualitative evidence synthesis methods for use in health technology assessments of complex interventions.* [Bremen (DE)]: INTEGRATE-HTA; 2016.

128. Ngai P, Kim G, Chak G, Lin K, Maeda M, Mosaed S. Outcome of primary trabeculotomy ab interno (Trabectome) surgery in patients with steroid-induced glaucoma. *Medicine.* 2016;95(50):e5383.

129. Critical Appraisal Skills Programme (CASP) qualitative research checklist. Oxford (GB): CASP UK; 2017: http://www.casp-uk.net/casp-tools-checklists. Accessed 2017 Sep 14.

130. Malterud K. Qualitative research: standards, challenges, and guidelines. *Lancet.* 2001;358(9280):483-488.

131. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC Med Res Methodol.* 2008;8:45.

132. Shoji N, Kasahara M, Iijima A, Takahashi M, Tatsui S, Matsumura K, et al. Short-term evaluation of Trabectome surgery performed on Japanese patients with open-angle glaucoma. *Jpn J Ophthalmol.* 2016;60(3):156-165.

133. Lacey J, Cate H, Broadway DC. Barriers to adherence with glaucoma medications: a qualitative research study. *Eye (Lond).* 2009;23(4):924-932.

134. Green J, Siddall H, Murdoch I. Learning to live with glaucoma: a qualitative study of diagnosis and the impact of sight loss. *Soc Sci Med.* 2002;55(2):257-267.

135. Cross V, Shah P, Glynn M, Chidrawar S. ReGAE 5: Can we improve the surgical journey for African-Caribbean patients undergoing glaucoma filtration surgery? Some preliminary findings. *Clin Ophthalmol.* 2009;3:1-12.

136. Leighton P, Lonsdale AJ, Tildsley J, King AJ. The willingness of patients presenting with advanced glaucoma to participate in a trial comparing primary medical vs primary surgical treatment. *Eye.* 2012;26(2):300-306.

137. Glen FC, Baker H, Crabb DP. A qualitative investigation into patients' views on visual field testing for glaucoma monitoring. *BMJ Open.* 2014;4(1):e003996.

138. Prior M, Francis JJ, Azuara-Blanco A, Anand N, Burr JM, Glaucoma screening Platform Study group. Why do people present late with advanced glaucoma? A qualitative interview study. *Br J Ophthalmol.* 2013;97(12):1574-1578.

139. Killeen OJ, MacKenzie C, Heisler M, Resnicow K, Lee PP, Newman-Casey PA. User-centered Design of the eyeGuide: A Tailored Glaucoma Behavior Change Program. *J Glaucoma.* 2016;25(10):815-821.

140. Glen FC, Crabb DP. Living with glaucoma: A qualitative study of functional implications and patients' coping behaviours. *BMC Ophthalmol.* 2015;15:128.

141. Burns J, Barrett G, Murdoch I. The experiences of patients with suspected glaucoma. A qualitative study. *Ophthalmic Nursing.* 2001;5(3):8-11.

142. Taylor SA, Galbraith SM, Mills RP. Causes of non-compliance with drug regimens in glaucoma patients: A qualitative study. *J Ocul Pharmacol Ther.* 2002;18(5):401-409.

143. Kugelmann R, Bensinger RE. Metaphors of glaucoma. *Cult Med Psychiatry.* 1983;7(3):313-328.

144. Newman-Casey PA, Shtein RM, Coleman AL, Herndon L, Lee PP. Why patients with glaucoma lose vision: The patient perspective. *J Glaucoma.* 2016;25(7):e668-e675.

145. Shtein RM, Newman-Casey PA, Herndon L, Coleman AL, Lee PP. Assessing the role of the family/support system perspective in patients with glaucoma. *J Glaucoma.* 2016;25(7):e676-e680.

146. Nordmann JP, Denis P, Vigneux M, Trudeau E, Guillemin I, Berdeaux G. Development of the conceptual framework for the Eye-Drop Satisfaction Questionnaire (EDSQ) in glaucoma using a qualitative study. *BMC Health Serv Res.* 2007;7:124.

147. Lunnela J, Kaariainen M, Kyngas H. The views of compliant glaucoma patients on counselling and social support. *Scand J Caring Sci.* 2010;24(3):490-498.

148. Vieira AAP, Guedes RAP, Vieira RCPA, Guedes VMP. Patient's perception on glaucoma and different types of treatment (medical versus surgical treatment). *Rev Bras Oftalmol.* 2015;74(4):235-240. http://www.scielo.br/scielo.php?pid=S0034-72802015000400235&script=sci_arttext&tlng=en. Accessed 2017 Dec 8.

149. Gramer E, Leydhecker W, Krieglstein GK. [The physician's obligation to educate patients - legal aspects - patients' expectations]. *Klin Monbl Augenheilkd.* 1982;181(1):46-53.

150. Zhang M, Wu X, Li L, Huang Y, Wang G, Lam J, et al. Understanding barriers to cataract surgery among older persons in rural China through focus groups. *Ophthalmic Epidemiol.* 2011;18(4):179-186.

151. McGrath C, Laliberte Rudman D, Polgar J, Spafford MM, Trentham B. Negotiating 'positive' aging in the presence of age-related vision loss (ARVL): The shaping and perpetuation of disability. *J Aging Stud.* 2016;39:1-10.

152. DiPietro C, Nale P. Trabecular bypass stents changing glaucoma practice. *Ocular Surgery News.* 2013;31(16):13-13.

153. Hebert A, Burns A, Garcia-Siekavizza A, Sherwood MB. Capturing the uncaptured: An anthropological approach to quality of life perception in glaucoma patients. *Investigative Ophthalmology & Visual Science.* 1996;37(3):s36.

154. Raj M, Wells S, Ford C. Minimally invasive glaucoma surgery in Canada: implementation considerations. *(CADTH Environmental scan no. 76)*. Ottawa (ON): CADTH; 2018: https://cadth.ca/minimally-invasive-glaucoma-surgery-implementation-considerations-0. Accessed 2018 May 16.

155. Reid L. Introduction to the special issue: Precarious solidarity-preferential access in Canadian health care. *Health Care Anal.* 2017;25(2):107-113.

156. Reid L. Medical need: Evaluating a conceptual critique of universal health coverage. *Health Care Anal.* 2017;25(2):114-137.

157. McAlister CN, Ahmed II. Noninsured services provided with insured cataract surgery in Canada: ensuring transparent and fair treatment for patients. *CMAJ.* 2015;187(11):813-816.

158. Canada Health Act (R.S.C., 1985, c.C-6). *Justice Laws Website*. Ottawa (ON): Government of Canada; 2018: http://laws-lois.justice.gc.ca/eng/acts/c-6/FullText.html. Accessed 2018 Jul 23 (Last amended on 2017 Dec 12).

159. Khan AM, Trope GE, Wedge R, Buys YM, El-Defrawy S, Chen Q, et al. Policy implications of regional variations in eye disease detection and treatment on Prince Edward Island: a repeated cross-sectional analysis, 2010-2012. *BMC Health Serv Res.* 2018;18(1):273, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5894155. Accessed 2018 May 3.

160. Jacobs DS. Open-angle glaucoma: epidemiology, clinical presentation, and diagnosis. Waltham (MA): UpToDate; 2018.

161. Ou Y. Glaucoma in the African American and Hispanic communities. Clarksburg (MD): BrightFocus Foundation; 2015: https://www.brightfocus.org/glaucoma/article/glaucoma-african-american-and-hispanic-communities. Accessed 2018 Jul 23.

162. Hark L, Waisbourd M, Myers JS, Henderer J, Crews JE, Saaddine JB, et al. Improving Access to Eye Care among Persons at High-Risk of Glaucoma in Philadelphia--Design and Methodology: The Philadelphia Glaucoma Detection and Treatment Project. *Ophthalmic Epidemiol.* 2016;23(2):122-130.

163. Nader N. High glaucoma prevalence in blacks leaves questions about treatment. *Ocular Surgery News*. Thorofare (NJ): Helio; 2003: https://www.healio.com/ophthalmology/glaucoma/news/print/ocular-surgery-news/%7Ba3d688a4-58d4-44f3-a3f8-7c8d2998a8bf%7D/high-glaucoma-prevalence-in-blacks-leaves-questions-about-treatment. Accessed 2018 Jul 23.

164. Waisbourd M, Pruzan NL, Johnson D, Ugorets A, Crews JE, Saaddine JB, et al. The Philadelphia Glaucoma Detection and Treatment Project: Detection Rates and Initial Management. *Ophthalmology.* 2016;123(8):1667-1674.

165. Taubenslag KJ, Kammer JA. Outcomes Disparities between Black and White Populations in the Surgical Management of Glaucoma. *Semin Ophthalmol.* 2016;31(4):385-393.

166. Do racial and gender disparities exist in newer glaucoma treatments? *EurekAlert!* New York (NY): American Association for the Advancement of Science; 2018: https://eurekalert.org/pub_releases/2018-03/aaoo-dra030218.php. Accessed 2018 Mar 2.

167. Truth and Reconciliation Commission of Canada: Calls To Action. Winnipeg (MB): Truth and Reconciliation Commission of Canada; 2015: http://www.trc.ca/websites/trcinstitution/File/2015/Findings/Calls_to_Action_English2.pdf. Accessed 2018 Jul 23.

168. Michaelov E, Armstrong JJ, Nguyen M, Instrum B, Lam T, Denstedt J, et al. Assessing the methodological quality of glaucoma clinical practice guidelines and their recommendations on microinvasive glaucoma surgery: A systematic review. *J Glaucoma.* 2018;27(2):e44-e49.

169. Broekman ML, Carriere ME, Bredenoord AL. Surgical innovation: the ethical agenda: A systematic review. *Medicine.* 2016;95(25):e3790.

170. Barnett SJ, Katz A. Patients as partners in innovation. *Semin Pediatr Surg.* 2015;24(3):141-144.

171. Johnson J, Rogers W. Innovative surgery: the ethical challenges. *J Med Ethics.* 2012;38(1):9-12.

172. Johnson J, Rogers W. Joint issues--conflicts of interest, the ASR hip and suggestions for managing surgical conflicts of interest. *BMC Med Ethics.* 2014;15:63.

173. Lee WT, Rocke D, Holsinger FC. Surgical innovation, industry partnership, and the enemy within. *Head Neck.* 2014;36(4):461-465.

174. Karpowicz L, Bell E, Racine E. Ethics Oversight Mechanisms for Surgical Innovation: A Systematic and Comparative Review of Arguments. *J Empir Res Hum Res Ethics.* 2016;11(2):135-164.

175. Geiger JD, Hirschl RB. Innovation in surgical technology and techniques: Challenges and ethical issues. *Semin Pediatr Surg.* 2015;24(3):115-121.

176. Angelos P. Surgical ethics and the challenge of surgical innovation. *Am J Surg.* 2014;208(6):881-885.

177. Pfadenhauer L, Rohwer A, Burns J, Booth A, Bakke Lysdahl K, HJofmann B, et al. Guidance for the assessment of context and implementation in Health Technology Assessments (HTA) and systematic reviews of complex interventions: the Context and Implementation of Complex Interventions (CICI) Framework. Integrated Health Technology Assessment for Evaluating Complex Technologies (INTEGRATE-HTA); 2016: http://www.integrate-hta.eu/wp-content/uploads/2016/02/Guidance-for-the-Assessment-of-Context-and-Implementation-in-HTA-and-Systematic-Reviews-of-Complex-Interventions-The-Co.pdf. Accessed 2018 Feb 12.

178. Ahmed I. A brief history of MIGS: the long and controversial journey to microinvasive glaucoma surgery (MIGS), and the quest to retire trabeculectomy. *The Ophthalmologist.* 2015(21):18-25. http://www.prismeyeinstitute.com/wp-content/uploads/2015/12/TOP_Issue_0715.pdf. Accessed 2018 Mar 28.

179. Szigiato AA, Sandhu S, Ratnarajan G, Dorey MW, Ahmed IIK. Surgeon perspectives on learning ab-interno gelatin microstent implantation. *Can J Ophthalmol.* 2018;53(3):246-251.

180. Szigiato AA, Trope GE, Jin Y, Buys YM. Trends in glaucoma surgical procedures in Ontario: 1992-2012. *Can J Ophthalmol.* 2015;50(5):338-344.

181. Chow JTY, Hutnik CML, Solo K, Malvankar-Mehta MS. When is evidence enough evidence? A systematic review and meta-analysis of the trabectome as a solo procedure in patients with primary open-angle glaucoma. *J Ophthalmol.* 2017;2017:2965725.

182. Grover DS. Expanding regimen with gel stent for surgical glaucoma management: Surgeon's brief learning period highlights ease of placing predictable, precise MIGS device. *Ophthalmology Times.* 2017;42(14):14-15.

183. Hovanesian JA. Three reasons why MIGS may replace glaucoma drops as first-line therapy. *Ocular Surgery News*. Thorofare (NJ): Helio; 2016: https://www.healio.com/ophthalmology/glaucoma/news/blogs/%7Bfdbc2a5f-d899-4228-b08b-b403113cacc5%7D/john-a-hovanesian-md-facs/blog-three-reasons-why-migs-may-replace-glaucoma-drops-as-first-line-therapy. Accessed 2016 Feb 26.

184. Krader CG. Making the move to MIGS. *Ophthalmology Times.* 2015. http://ophthalmologytimes.modernmedicine.com/ophthalmologytimes/news/making-move-migs. Accessed 2018 Jan 25.

185. Krader CG. Glaucoma specialists focus attention on forthcoming advances, therapies. *Ophthalmology Times*. 2014. http://www.ophthalmologytimes.com/modern-medicine-feature-articles/glaucoma-specialists-focus-attention-forthcoming-advances-therapies. Accessed 2018 Jan 25.

186. Rau M. Minimally invasive glaucoma surgery increasingly performed by anterior segment surgeons. *Ocular Surgery News*. Thorofare (NJ): Helio; 2016: https://www.healio.com/ophthalmology/glaucoma/news/print/ocular-surgery-news/%7Bea035f92-ca4b-4e7b-a765-0f4b970d4ede%7D/minimally-invasive-glaucoma-surgery-increasingly-performed-by-anterior-segment-surgeons?page=6. Accessed 2017 Nov 16.

187. Buznego C. Trabecular micro-bypass stent for glaucoma. *Tech Ophthalmol.* 2009;7(1):21-24.

188. Kaplowitz K, Schuman JS, Loewen NA. Techniques and outcomes of minimally invasive trabecular ablation and bypass surgery. *B J Ophthalmol.* 2014;98(5):579-585.

189. Loewen N, Fallano K, Bussel I, Kagemann L, Lathrop KL. Training strategies and outcomes of ab interno trabeculectomy with the trabectome. *F1000Research.* 2017;6:67.

190. Rodriguez-Una I, Azuara-Blanco A, King AJ. Survey of glaucoma surgical preferences and post-operative care in the United Kingdom. *Clin Exp Ophthalmol.* 2017;45(3):232-240.

191. Craven ER. Trabecular micro-bypass Shunt (iStent : Basic science, clinical, and future). *Middle East Afr J Ophthalmol.* 2015;22(1):30-37.

192. Iordanous Y, Hutnik CM, Malvankar-Mehta MS. Response to "Advancing the Economic Assessment of Microinvasive Glaucoma Surgery". *J Glaucoma.* 2016;25(7):e723-e724.

193. Canadian Ophthalmological Society (COS) & Canadian Glaucoma Society (CGS) micro-invasive or minimally invasive glaucoma surgery (MIGS) position statement. Canadian Glaucoma Society; 2017: http://cgs-scg.org/public-documents/2017/12/9/canadian-ophthalmological-society-cos-canadian-glaucoma-society-cgs-micro-invasive-or-minimally-invasive-glaucoma-surgery-migs-position-statement-december-2017. Accessed 2018 Feb 22.

194. Chadha N, Liu J, Maslin JS, Teng CC. Trends in ophthalmology resident surgical experience from 2009 to 2015. *Clin Ophthalmol.* 2016;10:1205-1208.

195. Miskala PH, Hawkins BS, Mangione CM, Bass EB, Bressler NM, Dong LM, et al. Responsiveness of the National Eye Institute Visual Function Questionnaire to changes in visual acuity: findings in patients with subfoveal choroidal neovascularization--SST Report No. 1. *Arch Ophthalmol.* 2003;121(4):531-539.

196. Suner IJ, Kokame GT, Yu E, Ward J, Dolan C, Bressler NM. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. *Invest Ophthalmol Vis Sci.* 2009;50(8):3629-3635.

197. Quaranta L, Riva I, Gerardi C, Oddone F, Floriano I, Konstas AG. Quality of Life in Glaucoma: A Review of the Literature. *Adv Ther.* 2016;33(6):959-981.

198. Medeiros FA. Biomarkers and Surrogate Endpoints: Lessons Learned From Glaucoma. *Invest Ophthalmol Vis Sci.* 2017;58(6):BIO20-BIO26.

199. Chauhan BC, Malik R, Shuba LM, Rafuse PE, Nicolela MT, Artes PH. Rates of glaucomatous visual field change in a large clinical population. *Invest Ophthalmol Vis Sci.* 2014;55(7):4135-4143.

200. Chansangpetch S, Lau K, Perez CI, Nguyen N, Porco TC, Lin SC. Efficacy of cataract surgery with trabecular micro-bypass stent implantation in combined-mechanism angle closure glaucoma patients. *Am J Ophthalmol.* 2018;195:191-198.

201. Directions for use / package insert: Glaukos Corporation iStent inject Trabecular Micro-Bypass System. *13. Clinical trial results*. San Clemente (CA): Glaukos Corporation: https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170043c.pdf. Accessed 2018 Oct 12.

202. SooHoo JR, Seibold LK, Kahook MY. Ab interno trabeculectomy in the adult patient. *Middle East Afr J Ophthalmol.* 2015;22(1):25-29.

203. Manasses DT, Au L. The new era of glaucoma micro-stent surgery. *Ophthalmol Ther.* 2016;5(2):135-146.

204. Hoh H, Grisanti S, Grisanti S, Rau M, Ianchulev S. Two-year clinical experience with the CyPass micro-stent: safety and surgical outcomes of a novel supraciliary micro-stent. *Klin Monbl Augenheilkd.* 2014;231(4):377-381.

205. Kent C. Glaucoma: in search of the perfect stent. *Review of Ophthalmology*. New York (NY): Jobson Medical Information LLC; 2015: https://www.reviewofophthalmology.com/article/glaucoma-in-search-of-the-perfect-stent. Accessed 2016 Dec 1.

206. Perez-Torregrosa VT, Olate-Perez A, Cerda-Ibanez M, Gargallo-Benedicto A, Osorio-Alayo V, Barreiro-Rego A, et al. Combined phacoemulsification and XEN45 surgery from a temporal approach and 2 incisions. *Arch Soc Esp Oftalmol.* 2016;91(9):415-421.

207. Sudesh S, Moseley MJ, Thompson JR. Accuracy of Goldmann tonometry in clinical practice. *Acta Ophthalmol (Copenh).* 1993;71(2):185-188.

208. Dielemans I, Vingerling JR, Hofman A, Grobbee DE, de Jong PT. Reliability of intraocular pressure measurement with the Goldmann applanation tonometer in epidemiological studies. *Graefes Arch Clin Exp Ophthalmol.* 1994;232(3):141-144.

209. Glaucoma: diagnosis and management. *(NICE clinical guideline; no. 81)*. London (GB): National Institute for Health and Care Excellence; 2017: https://www.nice.org.uk/guidance/NG81. Accessed 2018 Feb 1.

210. Boland MV, Ervin AM, Friedman DS, Jampel HD, Hawkins BS, Vollenweider D, et al. Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2013;158(4):271-279.

211. Maier PC, Funk J, Schwarzer G, Antes G, Falck-Ytter YT. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ.* 2005;331(7509):134.

212. Konstas AG, Maskaleris G, Gratsonidis S, Sardelli C. Compliance and viewpoint of glaucoma patients in Greece. *Eye (Lond).* 2000;14 Pt 5:752-756.

213. *R* [computer program]. Vienna (AUT): The R Foundation for Statistical Computing; 2018.

214. *RStudio* [computer program]. Boston (MA): RStudio, Inc.; 2015.

215. Lee R, Hutnik C. Projected cost comparison of selective laser trabeculoplasty versus glaucoma medication in the Ontario Health Insurance Plan. *Can J Ophthalmol.* 2006;41(1):449-456.

Appendix 1: Minimally Invasive Glaucoma Surgery Devices and Procedures of Interest

MIGS Device or Procedure	Description
Approach: Reducing Aqueous Production	
Endoscopic cyclophotocoagulation (or endocyclophotocoagulation) (ECP)	ECP involves targeted ablation of the ciliary body with an endoscope probe to reduce the production of aqueous humour.[12,14]
Approach: Increasing Trabecular Outflow by Bypassing the TM Using Tissue Ablation/Removal	
Trabectome	The Trabectome is a surgical device used to perform an "ab interno Trabeculectomy," which involves ablation and removal of tissue from the TM and inner wall of Schlemm's canal using high-frequency electrocautery to facilitate the outflow of aqueous humour from the anterior chamber to the collector channels.[12,23,126]
Kahook Dual Blade	The Kahook is a dual-blade single-use instrument designed to perform an ab interno Trabeculectomy, similar to the Trabectome. The instrument removes tissue from the TM and inner wall of Schlemm's canal to create a pathway for improving aqueous outflow.[202]
Approach: Increasing Trabecular Outflow by Bypassing the TM Using a Device	
iStent (first generation)	The iStent is a device made of heparin-coated titanium that is inserted into Schlemm's canal using an ab interno surgical technique to create a permanent bypass channel for aqueous outflow from the anterior chamber to the collector channels.[12,19,23,30] Single or multiple iStents may be implanted.[23]
iStent Inject (second generation)	The iStent Inject is also made of heparin-coated titanium, but is three times smaller than the first-generation iStent, and is designed for ab interno injection into Schlemm's canal using a less challenging surgical technique.[22] The iStent Inject is preloaded with two stents, such that both can be placed without removing the injector from the eye.[22]
Hydrus Microstent	The Hydrus Microstent is an 8 mm long curved intracanalicular scaffold that is implanted into Schlemm's canal to maintain patency and aqueous flow through the TM and collector channels.[62,71]
Approach: Increasing Trabecular Outflow by Bypassing the TM Via 360° Suture	
Gonioscopy-assisted transluminal trabeculotomy (GATT)	GATT is a procedure for ab interno circumferential trabeculotomy using a 360° suture or microcatheter in Schlemm's canal (i.e., opening the trabecular meshwork pathway without removing tissue).[35,202]
Approach: Increasing Uveoscleral Outflow Via Suprachoroidal Shunts	
CyPass Micro-Stent[a]	The CyPass Micro-Stent is a polyamide tube, 6.35 mm long with a 300 mm lumen,[203] that is implanted into the supraciliary space (between the ciliary body and the sclera)[203] to create a permanent channel between the anterior chamber and the suprachoroidal space.[12,204]
Approach: Creating a Subconjunctival Pathway for Filtration	
XEN 45 Gel Stent **XEN 63 Gel Stent** **XEN 140 Gel Stent**	The XEN Gel Stent is a device that is implanted from the anterior chamber into the subconjunctival space to provide a bypass route for aqueous outflow. The cylindrical implant is made of flexible collagen-derived gelatin material cross-linked with glutaraldehyde,[203] measures 6 mm in length, and is available in three different options denoted by inner diameters of 45 µm, 63 µm, and 140 µm.[12,205,206] However, the manufacturer recommends only the 45 µm size to prevent hypotony.[203] The procedure may be augmented with subconjunctival injection of mitomycin C to reduce scarring.[203]

ECP = endoscopic cyclophotocoagulation; GATT = gonioscopy-assisted transluminal trabeculotomy; MIGS = minimally invasive glaucoma surgery; TM = trabecular meshwork.

[a] The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the Medical Devices Active Licence Listing and is therefore included in this report.

Appendix 2: Literature Search Strategies

Clinical Review

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to Present Ovid MEDLINE 1946 to Present Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 30, 2017
Alerts:	Monthly search updates until project completion.
Study Types:	No filters used
Limits:	Publication years 2000 forward English or French language Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.dv	Device name (Embase)
ppez	Ovid database code; Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
1	exp Glaucoma/ or exp Glaucoma Drainage Implants/ or exp Sclerostomy/ or exp Trabeculectomy/
2	(glaucoma* or antiglaucoma*).ti,ab,kf.
3	((open or close or closed or OAG or CAG or POAG or COAG) adj5 angle* adj5 (eye or eyes or ocular*)).ti,ab,kf.
4	(glaucoma* or opthalmol*).jw.
5	1 or 2 or 3 or 4
6	exp Microsurgery/ or exp Minimally Invasive Surgical Procedures/ or stents/

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
7	((Minimal* or Minimiz*or minimis* or micro*) adj5 (incision* or invasive* or penetrat* or surgery or surgeries)).ti,ab,kf.
8	(Microinvasive or micro-invasive or microincision* or micro-incision* or micro bypass* or microbypass* or small incision* or micro-surg* or microsurg* or MicroPulse or micro pulse or non penetrat* or nonpenetrat* or less invasive or mini device* or minidevice*).ti,ab,kf.
9	(stent* or microstent* or microshunt* or shunt*or dual blade or dualblade or duo blade or duoblade or micro blade or microblade or scaffold* or microscaffold*).ti,ab,kf.
10	MIGS.ti,ab,kf.
11	(Trabectome or Ab interno or XGEN or Xen* or iStent or I stent or hydrus or Aquashunt or STARflo or Esnoper-Clip or Cypass or infocus or SOLX or gel stent* or gelatin stent* or canalicular scaffolding or Kahook).ti,ab,kf.
12	((Gonioscopy adj5 Trabeculotomy) or GATT).ti,ab,kf.
13	(Excimer adj5 laser adj5 trabeculotom*).ti,ab,kf.
14	(Endocyclophotocoagulation* or (Cyclophotocoagulation adj5 endoscop*)).ti,ab,kf.
15	Endoscope-assisted goniosynechialysis.ti,ab,kf.
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	5 and 16
18	17 use ppez
19	exp glaucoma drainage implant/ or exp glaucoma/ or exp glaucoma surgery/ or exp sclerostomy/ or exp trabeculectomy/
20	(glaucoma* or antiglaucoma*).ti,ab,kw.
21	((open or close or closed or OAG or CAG or POAG or COAG) adj5 angle* adj5 (eye or eyes or ocular*)).ti,ab,kw.
22	(glaucoma* or opthalmol*).jw.
23	19 or 20 or 21 or 22
24	exp microsurgery/ or exp minimally invasive surgery/ or exp minimally invasive procedure/ or exp stent/
25	((Minimal* or Minimiz*or minimis* or micro*) adj5 (incision* or invasive* or penetrat* or surgery or surgeries)).ti,ab,kw.
26	(Microinvasive or micro-invasive or microincision* or micro-incision* or micro bypass* or microbypass* or small incision* or micro-surg* or microsurg* or MicroPulse or micro pulse or non penetrat* or nonpenetrat* or less invasive or mini device* or minidevice*).ti,ab,kw.
27	(stent* or microstent* or microshunt* or shunt*or dual blade or dualblade or duo blade or duoblade or micro blade or microblade or scaffold* or microscaffold*).ti,ab,kw,dv.
28	MIGS.ti,ab,kw,dv.
29	(Trabectome or Ab interno or XGEN or Xen* or iStent or I stent or hydrus or Aquashunt or STARflo or Esnoper-Clip or Cypass or infocus or SOLX or gel stent* or gelatin stent* or canalicular scaffolding or Kahook).ti,ab,kw,dv.
30	((Gonioscopy adj5 Trabeculotomy) or GATT).ti,ab,kw,dv.
31	(Excimer adj5 laser adj5 trabeculotom*).ti,ab,kw,dv.
32	(Endocyclophotocoagulation* or (Cyclophotocoagulation adj5 endoscop*)).ti,ab,kw,dv.
33	Endoscope-assisted goniosynechialysis.ti,ab,kw,dv.
34	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	23 and 34
36	35 use oemezd
37	18 or 36
38	37 not conference abstract.pt.
39	exp animals/

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy**
40	exp animal experimentation/ or exp animal experiment/
41	exp models animal/
42	nonhuman/
43	exp vertebrate/ or exp vertebrates/
44	or/39-43
45	exp humans/
46	exp human experimentation/ or exp human experiment/
47	or/45-46
48	44 not 47
49	38 not 48
50	limit 49 to yr="2000 -Current"
51	limit 50 to english language
52	50 and french.lg.
53	51 or 52
54	remove duplicates from 53

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane DARE via Wiley	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.	
Cochrane Database of Systematic Reviews via Wiley	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.	
Cochrane Central Via Ovid	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions.	
CINAHL (EBSCO interface)	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform.	

Grey Literature

Dates for Search:	December 2017
Keywords:	Included terms for minimally invasive glaucoma surgeries and devices
Limits:	Publication years 2000 to present; English or French language

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

Patients' Perspectives and Experiences Review

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE 1946 to Present Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	August 31, 2017 November 20, 2017
Alerts:	Monthly search updates until project completion.
Study Types:	Qualitative, including questionnaires and surveys
Limits:	Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type

MULTI-DATABASE STRATEGY

#	Patients' Perspectives Search Strategy #1 – August 31, 2017
1	exp Glaucoma/
2	(glaucoma* or antiglaucoma*).ti,ab,kf.
3	((open or close or closed or OAG or CAG or POAG or COAG) adj5 angle* adj5 (eye or eyes or ocular*)).ti,ab,kf.
4	glaucoma*.jw.
5	1 or 2 or 3 or 4
6	exp Glaucoma Drainage Implants/ or exp Filtering Surgery/ or exp Sclerostomy/ or exp Trabeculectomy/ or exp Stents/
7	MIGS.ti,ab,kf.
8	(Trabectome or Ab interno or XGEN stent* or XGEN gel stent* or XEN implant or XEN glaucoma implant or Xen 45 gel stent or iStent or I stent or hydrus or Aquashunt or STARflo or Esnoper-Clip or Cypass or infocus or SOLX or gel stent* or gelatin stent* or canalicular scaffolding).ti,ab,kf.
9	((glaucoma* or antiglaucoma* or eye or eyes or ocular*) and (duoblade or duo blade)).ti,ab,kf.
10	((Glaucoma* or antiglaucoma*) and (shunt* or stent*)).ti,ab,kf.

MULTI-DATABASE STRATEGY	
11	(Gonioscopy*adj5 Trabeculotom* or GATT).ti,ab,kf.
12	(Excimer adj5 laser adj5 trabeculotom*).ti,ab,kf.
13	(Endocyclophotocoagulation* or (Cyclophotocoagulation adj5 endoscop*)).ti,ab,kf.
14	Endoscope assisted goniosynechialysis.ti,ab,kf.
15	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	exp Empirical Research/ or Interview/ or Interviews as Topic/ or Personal Narratives/ or Focus Groups/ or Narration/ or Nursing Methodology Research/
17	Interview/
18	interview*.ti,ab,kf.
19	qualitative.ti,ab,kf,jn.
20	(theme* or thematic).ti,ab,kf.
21	ethnological research.ti,ab,kf.
22	ethnograph*.ti,ab,kf.
23	ethnonursing.ti,ab,kf.
24	phenomenol*.ti,ab,kf.
25	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf.
26	(life stor* or women* stor*).ti,ab,kf.
27	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf.
28	(data adj1 saturat$).ti,ab,kf.
29	participant observ*.ti,ab,kf.
30	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf.
31	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf.
32	(humanistic or existential or experiential or paradigm*).ti,ab,kf.
33	(field adj (study or studies or research)).ti,ab,kf.
34	human science.ti,ab,kf.
35	biographical method.ti,ab,kf.
36	theoretical sampl*.ti,ab,kf.
37	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf.
38	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf.
39	(life world or life-world or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf.
40	((lived or life) adj experience*).ti,ab,kf.
41	cluster sampl*.ti,ab,kf.
42	observational method*.ti,ab,kf.
43	content analysis.ti,ab,kf.
44	(constant adj (comparative or comparison)).ti,ab,kf.
45	((discourse* or discurs*) adj3 analys?s).ti,ab,kf.
46	narrative analys?s.ti,ab,kf.
47	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.
48	(van adj manen*).ti,ab,kf.
49	(van adj kaam*).ti,ab,kf.
50	(corbin* adj2 strauss*).ti,ab,kf.
51	or/16-50
52	5 and 51

MULTI-DATABASE STRATEGY	
53	15 and 51
54	52 or 53
#	**Patients' Perspectives Search Strategy #2 – November 20, 2017**
1	exp Glaucoma/
2	(glaucoma* or antiglaucoma*).ti,ab,kf.
3	((open or close or closed or OAG or CAG or POAG or COAG) adj5 angle* adj5 (eye or eyes or ocular*)).ti,ab,kf.
4	glaucoma*.jw.
5	1 or 2 or 3 or 4
6	exp Glaucoma Drainage Implants/ or exp Filtering Surgery/ or exp Sclerostomy/ or exp Trabeculectomy/ or exp Stents/
7	MIGS.ti,ab,kf.
8	((Trabectome or Ab interno or XGEN or XEN or iStent or I stent or hydrus or Aquashunt or STARflo or Esnoper-Clip or Cypass or infocus or SOLX or gel stent* or gelatin stent* or canalicular scaffolding) and (glaucoma* or antiglaucoma* or eye or eyes or ocular*)).ti,ab,kf.
9	((glaucoma* or antiglaucoma* or eye or eyes or ocular*) and (duoblade or duo blade)).ti,ab,kf.
10	((Glaucoma* or antiglaucoma*) and (shunt* or stent*)).ti,ab,kf.
11	(Gonioscopy*adj5 Trabeculotom* or GATT).ti,ab,kf.
12	(Excimer adj5 laser adj5 trabeculotom*).ti,ab,kf.
13	(Endocyclophotocoagulation* or (Cyclophotocoagulation adj5 endoscop*)).ti,ab,kf.
14	Endoscope assisted goniosynechialysis.ti,ab,kf.
15	(minimally invasive adj3 glaucoma).ti,ab,kf.
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	exp Cataract Extraction/
18	(cataract* adj5 (extract* or remov* or surger* or procedur* or operation or operations or minimally invasive)).ti,ab,kf.
19	exp Cataract/ and (exp Minimally Invasive Surgical Procedures/ or exp Specialties, Surgical/ or exp Surgical Procedures, Operative/)
20	exp Cataract/ and (extract* or remov* or surger* or procedur* or minimally invasive or operation or operations).ti,ab,kf.
21	(Intra ocular lens* or intraocular lens* or ((IOL or IOLs) adj3 lens*)).ti,ab,kf.
22	(lens* adj4 implant*).ti,ab,kf.
23	Phacoemulsification.ti,ab,kf.
24	(capsulotomy or capsulotomies).ti,ab,kf.
25	(phaco and cataract*).ti,ab,kf.
26	(Femtosecond laser and cataract*).ti,ab,kf.
27	(ECCE and cataract*).ti,ab,kf.
28	(ICCE and cataract*).ti,ab,kf.
29	(MSICS and cataract*).ti,ab,kf.
30	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	exp Empirical Research/ or Interview/ or Interviews as Topic/ or Personal Narratives/ or Focus Groups/ or Narration/ or Nursing Methodology Research/
32	Interview/
33	interview*.ti,ab,kf.
34	qualitative.ti,ab,kf,jw.
35	(theme* or thematic).ti,ab,kf.
36	ethnological research.ti,ab,kf.
37	ethnograph*.ti,ab,kf.

MULTI-DATABASE STRATEGY	
38	ethnomedicine.ti,ab,kf.
39	ethnonursing.ti,ab,kf.
40	phenomenol*.ti,ab,kf.
41	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf.
42	(life stor* or women* stor*).ti,ab,kf.
43	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf.
44	(data adj1 saturat$).ti,ab,kf.
45	participant observ*.ti,ab,kf.
46	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf.
47	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf.
48	(humanistic or existential or experiential or paradigm*).ti,ab,kf.
49	(field adj (study or studies or research or work)).ti,ab,kf.
50	(human science or social science).ti,ab,kf.
51	biographical method.ti,ab,kf.
52	theoretical sampl*.ti,ab,kf.
53	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf.
54	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf.
55	(life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf.
56	((lived or life) adj experience*).ti,ab,kf.
57	cluster sampl*.ti,ab,kf.
58	observational method*.ti,ab,kf.
59	content analysis.ti,ab,kf.
60	(constant adj (comparative or comparison)).ti,ab,kf.
61	((discourse* or discurs*) adj3 analys?s).ti,ab,kf.
62	narrative analys?s.ti,ab,kf.
63	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.
64	(van adj manen*).ti,ab,kf.
65	(van adj kaam*).ti,ab,kf.
66	(corbin* adj2 strauss*).ti,ab,kf.
67	or/31-66
68	5 and 67
69	16 and 67
70	30 and 67
71	68 or 69 or 70
72	"Surveys and Questionnaires"/
73	Health Care Surveys/
74	self report/
75	questionnaire*.ti,ab,kf.
76	survey*.ti,ab,kf.
77	or/72-76
78	5 and 77
79	16 and 77
80	30 and 77

MULTI-DATABASE STRATEGY	
81	78 or 79 or 80
82	71 or 81
83	exp animals/
84	exp animal experimentation/ or exp animal experiment/
85	exp models animal/
86	nonhuman/
87	exp vertebrate/ or exp vertebrates/
88	or/83-87
89	exp humans/
90	exp human experimentation/ or exp human experiment/
91	or/89-90
92	88 not 91
93	82 not 92

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane DARE via Wiley	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.	
Cochrane Database of Systematic Reviews via Wiley	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.	
Cochrane Central Via Ovid	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions.	
Scopus	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Scopus platform.	
CINAHL (EBSCO interface)	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform.	

Grey Literature

Dates for Search:	December 2017
Keywords:	Included terms for minimally invasive glaucoma surgeries and devices
Limits:	Publication years 2000 to present; English or French language

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

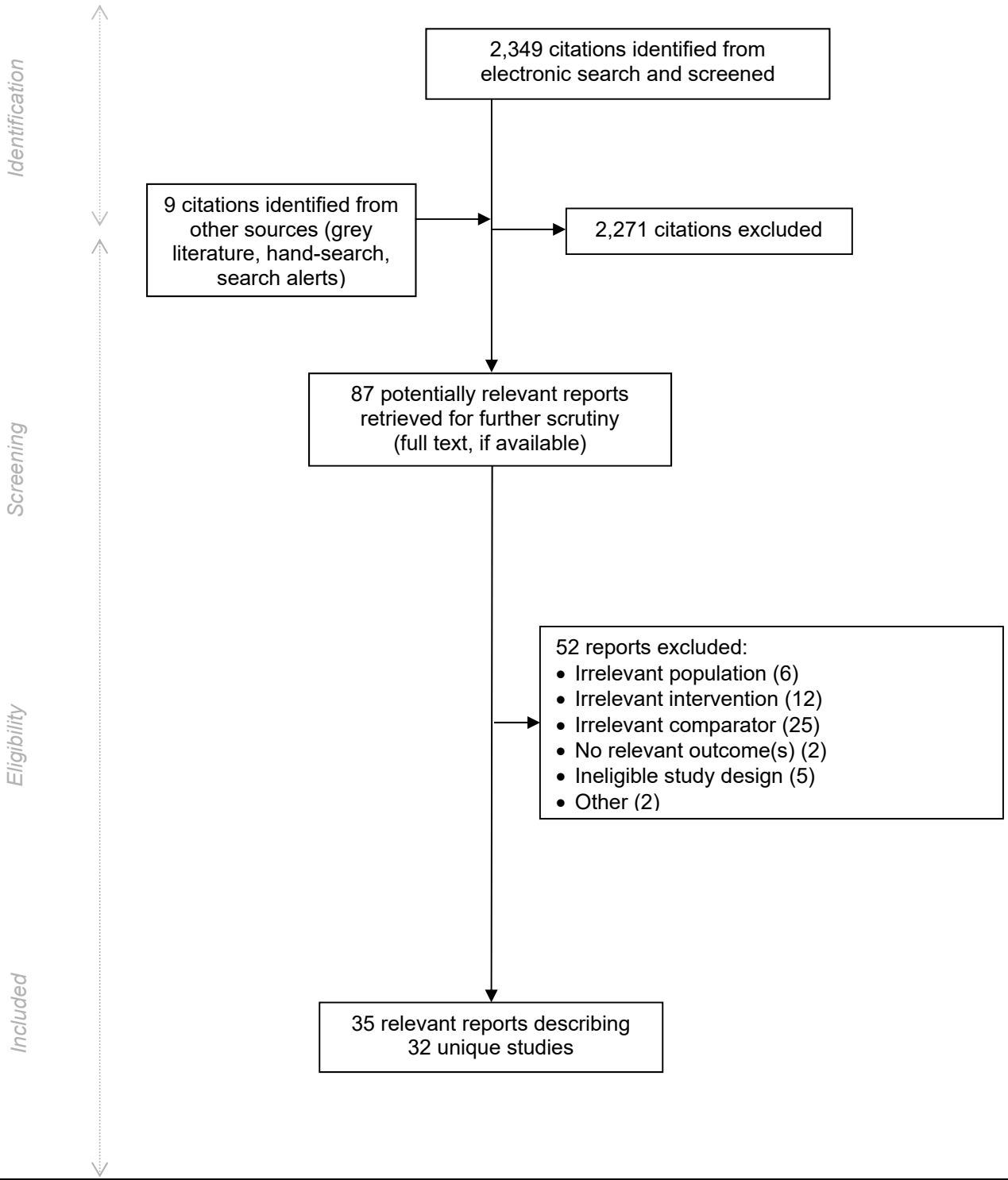
Appendix 3: Major and Minor Adverse Events — Clinical Review

Table 27: Categorization of Severity of Adverse Events or Complications

Minor Adverse Events or Complications	Major Adverse Events or Complications
• Bandage contact lens • Bleb leak • Blebitis • Blood clot • Conjunctival and tenon buttonhole • Conjunctivitis, allergic, or not specified • Corneal abrasion • Corneal edema, transient or not further specified • Corneal touch • Cyclodialysis cleft • Cystic bleb • Cystoid macular edema or macular edema • Decrease in visual acuity, temporary • Dellen • Diplopia, blurry vision, visual disturbance • Endothelial touch • Epiretinal membrane • Eye burning, soreness, discomfort, dry eye • Fibrin reaction • (Focal) Peripheral anterior synechiae • Foreign body sensation • Hemorrhage: ○ Disc hemorrhage ○ Subconjunctival hemorrhage ○ Vitreous hemorrhage • Hyphema (anterior-chamber hemorrhage) • Hypotony, early • Inflammatory precipitates in anterior chamber, iritis, uveitis (anterior or not further specified) • IOP decompensation • IOP spike or raised IOP, not further specified • IOP spike, early • Iridodialysis with no post-operative ocular sequelae • Iris atrophy • Iris incarceration • Iris touch • Laser suture lysis • Posterior capsular opacification • Progression of cataract • Ruptured capsule • Serous choroidal effusion, choroidal effusion, choroidals, choroidal folds, choroidal detachment • Shallow anterior chamber, reversed or not further specified • Stent not visible, blocked stent, exposed stent, stent malposition, unsuccessful stent implantation, intraoperative stent removal and replacement, stent not seated well • Tube block • Vitreal macular traction • Vitreous removal/vitrectomy, vitreous detachment • Wound leak or dehiscence	• Angle closure • Anterior ischemic optic neuropathy • Bullous keratopathy • Central retinal vein occlusion • Coreneal decompensation • Corneal edema, persistent • Decrease in visual acuity, unresolved or duration not specified • Development of neovascular glaucoma and secondary angle closure • Endophthalmitis • Failure of corneal graft • Hypotony maculopathy • Hypotony, not further specified, or persistent • Iris touch to the cornea • Malignant glaucoma • Phthisis bulbi • Posterior uveitis • Requirement for intracameral tissue plasminogen activator injection with synechiolysis • Requirement for penetrating keratoplasty • Retinal detachment • Shallow anterior chamber, complete collapse • Suprachoroidal hemorrhage • Tube exposure • Visual field loss

Appendix 4: Study Selection Flow Diagram — Clinical Review

Figure 26: PRISMA Flowchart of Selected Reports for the Clinical Review



Appendix 5: List of Included Studies — Clinical Review

1. Samuelson TW, Chang DF, Marquis R, Flowers B, Lim KS, Ahmed IIK, et al. A Schlemm Canal Microstent for Intraocular Pressure Reduction in Primary Open-Angle Glaucoma and Cataract: The HORIZON Study. Ophthalmology. 2018 Jun 23.
2. Moghimi S, Hamzeh N, Mohammadi M, Khatibi N, Bowd C, Weinreb RN. Combined glaucoma and cataract surgery: comparison of viscocanalostomy, endocyclophotocoagulation, and ab interno trabeculectomy. J Cataract Refract Surg. 2018 May;44(5):557-65.
3. Kinoshita-Nakano E, Nakanishi H, Ohashi-Ikeda H, Morooka S, Akagi T. Comparative outcomes of trabeculotomy ab externo versus trabecular ablation ab interno for open angle glaucoma. Jpn J Ophthalmol. 2018;1-8.
4. Fea AM, Ahmed II, Lavia C, Mittica P, Consolandi G, Motolese I, et al. Hydrus microstent compared to selective laser trabeculoplasty in primary open angle glaucoma: one year results. Clin Exp Ophthalmol [Internet]. 2017 Mar [cited 2017 Dec 6];45(2):120-7.
5. Ferguson TJ, Swan R, Sudhagoni R, Berdahl JP. Microbypass stent implantation with cataract extraction and endocyclophotocoagulation versus microbypass stent with cataract extraction for glaucoma. J Cataract Refract Surg. 2017 Mar;43(3):377-82.
6. Gonnermann J, Bertelmann E, Pahlitzsch M, Maier-Wenzel AB, Torun N, Klamann MK. Contralateral eye comparison study in MICS & MIGS: Trabectome(R) vs. iStent inject(R). Graefes Arch Clin Exp Ophthalmol. 2017 Feb;255(2):359-65.
7. Kang S, Luk S, Han H, Cordeiro MF, Ahmed F, Bloom P, et al. Refractive outcome of combined phacoemulsification and endoscopic cyclophotocoagulation. Int Ophthalmol. 2017 Dec;37(6):1311-7.
8. Kurji K, Rudnisky CJ, Rayat JS, Arora S, Sandhu S, Damji KF, et al. Phaco-trabectome versus phaco-iStent in patients with open-angle glaucoma. Can J Ophthalmol. 2017 Feb;52(1):99-106.
9. Marco S, Damji KF, Nazarali S, Rudnisky CJ. Cataract and Glaucoma Surgery: Endoscopic Cyclophotocoagulation versus Trabeculectomy. Middle East Afr J Ophthalmol [Internet]. 2017 Oct [cited 2018 Mar 7];24(4):177-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5793448
10. Murakami Y, Akil H, Chahal J, Dustin L, Tan J, Chopra V, et al. Endoscopic cyclophotocoagulation versus second glaucoma drainage device after prior aqueous tube shunt surgery. Clin Exp Ophthalmol. 2017 Apr;45(3):241-6.
11. Pahlitzsch M, Klamann MK, Pahlitzsch ML, Gonnermann J, Torun N, Bertelmann E. Is there a change in the quality of life comparing the micro-invasive glaucoma surgery (MIGS) and the filtration technique trabeculectomy in glaucoma patients? Graefes Arch Clin Exp Ophthalmol. 2017 Feb;255(2):351-7.
12. Perez Bartolome F, Rodrigues IA, Goyal S, Block E, Lim S, Alaghband P, et al. Phacoemulsification plus endoscopic cyclophotocoagulation versus phacoemulsification alone in primary open-angle glaucoma. Eur J Ophthalmol. 2017 Oct 25;0.
13. Schlenker MB, Gulamhusein H, Conrad-Hengerer I, Somers A, Lenzhofer M, Stalmans I, et al. Efficacy, safety, and risk factors for failure of standalone ab interno gelatin microstent implantation versus standalone trabeculectomy. Ophthalmology. 2017 Jun 7;124(11):1579-88.
14. Vlasov A, Kim WI. The efficacy of two trabecular bypass stents compared to one in the management of open-angle glaucoma. Mil Med. 2017 Mar;182(S1):222-5.
15. Vold S, Ahmed II, Craven ER, Mattox C, Stamper R, Packer M, et al. Two-year COMPASS trial results: Supraciliary microstenting with phacoemulsification in patients with open-angle glaucoma and cataracts. Ophthalmology. 2016 Oct;123(10):2103-12.
16. Katz LJ, Erb C, Carceller GA, Fea AM, Voskanyan L, Giamporcaro JE, 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 [Internet]. 2018 [cited 2018 Mar 7];12:255-62. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5798569
17. Katz LJ, Erb C, Carceller GA, Fea AM, Voskanyan L, Wells JM, et al. Prospective, randomized study of one, two, or three trabecular bypass stents in open-angle glaucoma subjects on topical hypotensive medication. Clin Ophthalmol [Internet]. 2015 [cited 2017 Dec 21];9:2313-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4686332

18. Vold SD, Voskanyan L, Tetz M, Auffarth G, Masood I, Au L, et al. Newly diagnosed primary open-angle glaucoma randomized to 2 trabecular bypass stents or prostaglandin: Outcomes through 36 months. Ophthalmol Ther [Internet]. 2016 Dec [cited 2017 Dec 21];5(2):161-72. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5125126
19. El Wardani M, Bergin C, Achache F, Sharkawi E. Evaluating the trabecular micro-bypass stent combined with phacoemulsification compared to phacoemulsification alone. Klin Monbl Augenheilkd. 2015 Apr;232(4):442-5.
20. Fea AM, Consolandi G, Zola M, Pignata G, Cannizzo P, Lavia C, et al. Micro-bypass implantation for primary open-angle glaucoma combined with phacoemulsification: 4-year follow-up. J Ophthalmol [Internet]. 2015 [cited 2017 Dec 21];2015:795357. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4637500
21. Khan M, Saheb H, Neelakantan A, Fellman R, Vest Z, Harasymowycz P, et al. Efficacy and safety of combined cataract surgery with 2 trabecular microbypass stents versus ab interno trabeculotomy. J Cataract Refract Surg. 2015 Aug;41(8):1716-24.
22. Pfeiffer N, Garcia-Feijoo J, Martinez-de-la-Casa JM, Larrosa JM, Fea A, Lemij H, et al. A randomized trial of a Schlemm's canal microstent with phacoemulsification for reducing intraocular pressure in open-angle glaucoma. Ophthalmology. 2015 Jul;122(7):1283-93.
23. Sheybani A, Saboori M, Kim JM, Gammon H, Lee AY, Bhorade AM. Effect of endoscopic cyclophotocoagulation on refractive outcomes when combined with cataract surgery. Can J Ophthalmol. 2015 Jun;50(3):197-201.
24. Siegel MJ, Boling WS, Faridi OS, Gupta CK, Kim C, Boling RC, et al. Combined endoscopic cyclophotocoagulation and phacoemulsification versus phacoemulsification alone in the treatment of mild to moderate glaucoma. Clin Experiment Ophthalmol. 2015 Aug;43(6):531-9.
25. Fea AM, Belda JI, Rekas M, Junemann A, Chang L, Pablo L, et al. Prospective unmasked randomized evaluation of the iStent inject® versus two ocular hypotensive agents in patients with primary open-angle glaucoma. Clin Ophthalmol [Internet]. 2014 [cited 2017 Dec 21];8:875-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4019628
26. Francis BA, Berke SJ, Dustin L, Noecker R. Endoscopic cyclophotocoagulation combined with phacoemulsification versus phacoemulsification alone in medically controlled glaucoma. J Cataract Refract Surg. 2014 Aug;40(8):1313-21.
27. Belovay GW, Naqi A, Chan BJ, Rateb M, Ahmed II. Using multiple trabecular micro-bypass stents in cataract patients to treat open-angle glaucoma. J Cataract Refract Surg. 2012 Nov;38(11):1911-7.
28. Craven ER, Katz LJ, Wells JM, Giamporcaro JE, iStent Study Group. Cataract surgery with trabecular micro-bypass stent implantation in patients with mild-to-moderate open-angle glaucoma and cataract: two-year follow-up. J Cataract Refract Surg. 2012 Aug;38(8):1339-45.
29. Jea SY, Francis BA, Vakili G, Filippopoulos T, Rhee DJ. Ab interno trabeculectomy versus trabeculectomy for open-angle glaucoma. Ophthalmology. 2012 Jan;119(1):36-42.
30. Samuelson TW, Katz LJ, Wells JM, Duh YJ, Giamporcaro JE, US iStent Study Group. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology. 2011 Mar;118(3):459-67.
31. Fea AM. Phacoemulsification versus phacoemulsification with micro-bypass stent implantation in primary open-angle glaucoma: randomized double-masked clinical trial. J Cataract Refract Surg. 2010 Mar;36(3):407-12.
32. Fernandez-Barrientos Y, Garcia-Feijoo J, Martinez-de-la-Casa JM, Pablo LE, Fernandez-Perez C, Garcia SJ. Fluorophotometric study of the effect of the glaukos trabecular microbypass stent on aqueous humor dynamics. Invest Ophthalmol Vis Sci. 2010 Jul;51(7):3327-32.
33. Lima FE, Magacho L, Carvalho DM, Susanna R, Avila MP. A prospective, comparative study between endoscopic cyclophotocoagulation and the Ahmed drainage implant in refractory glaucoma. J Glaucoma. 2004 Jun;13(3):233-7.
34. Dorairaj SK, Kahook MY, Williamson BK, Seibold LK, El Mallah MK, Singh IP. A multicenter retrospective comparison of goniotomy versus trabecular bypass device implantation in glaucoma patients undergoing cataract extraction. Clin Ophthalmol. 2018;12:791-97.
35. Ting JLM, Rudnisky CJ, Damji KF. Prospective randomized controlled trial of phaco-trabectome versus phaco-trabeculectomy in patients with open angle glaucoma. Can J Ophthalmol. 2018.

Appendix 6: List of Excluded Studies and Reasons for Exclusion — Clinical Review

Irrelevant Population:

1. **Dahan,E.**. What should be done when surgery fails? Congenital Glaucoma: IOP rises years after surgery. *Journal Francais d'Ophtalmologie.* 2006. 29 (2): 57-60.
2. **Hou X,Hu D,Cui Z,Zhou J,Cai L,Wang Y.**. Small-incision phacotrabeculectomy versus phacoemulsification in refractory acute primary angle closure with cataract. *BMC Ophthalmology [electronic resource].* 2015.15:88, 2015.
3. **LuebkeJ,BoehringerD,NeuburgerM,AntonA,WeckerT,CakirB,ReinhardT,JordanJ.F.**. Refractive and visual outcomes after combined cataract and trabectome surgery: A report on the possible influences of combining cataract and trabectome surgery on refractive and visual outcomes. *Graefes Arch Clin Exp Ophthalmol.* 2014. 253(3).
4. **Schaub F,Adler W,Koenig M.C.,Enders,P Dietlein,T.S.,Cursiefen,C,Heindl,L.M**. Combined Ab Interno Glaucoma Surgery Does not Increase the Risk of Pseudophakic Cystoid Macular Edema in Uncomplicated Eyes. *J Glaucoma.* 2017 Mar;26(3):227-232.
5. **Weiner Y,Severson M.L.,Weiner A.** Intraocular pressure 3 to 4 hours and 20 hours after cataract surgery with and without ab interno trabeculectomy. *Journal of Cataract and Refractive Surgery.* 2015. 41(10):2081-2091.
6. **Alnawaiseh M, Müller V, Lahme L, Merté RL, Eter N.** Changes in Flow Density Measured Using Optical Coherence Tomography Angiography after iStent Insertion in Combination with Phacoemulsification in Patients with Open-Angle Glaucoma. J Ophthalmol. 2018.

Irrelevant Intervention:

7. **Bull H,Von Wolff K, Korber N,Tetz M.** Three-year canaloplasty outcomes for the treatment of open-angle glaucoma: European study results. *Graefes Arch Clin Exp Ophthalmol.* 2011. 240(10):1537-1545.
8. **Gandolfi SA, Ungaro N, Ghirardini S, Tardini MG, Mora P.** Comparison of Surgical Outcomes between Canaloplasty and Schlemm's Canal Scaffold at 24 Months' Follow-Up. J Ophthalmol. 2016;2016:3410469.
9. **Gedde,S.J.** Results from the tube versus trabeculectomy study. Middle East Afr J Ophthalmol. 2009;16(3):107-111.
10. **Krix-Jachym K, Zarnowski T, Rekas M.** Risk Factors of Malignant Glaucoma Occurrence after Glaucoma Surgery. J Ophthalmol. 2017;2017:9616738.
11. **Klink T, Sauer J, Korber NJ, et al.** Quality of life following glaucoma surgery: canaloplasty versus trabeculectomy. Clin Ophthalmol. 2015;9:7-16.
12. **Koerber NJ.** Canaloplasty in one eye compared with viscocanalostomy in the contralateral eye in patients with bilateral open-angle glaucoma. Journal of Glaucoma. 2012;21(2):129-134.
13. **Tanito M, Matsuzaki Y, Ikeda Y, Fujihara E.** Comparison of surgically induced astigmatism following different glaucoma operations. Clin Ophthalmol. 2017;11:2113-2120.
14. **Park AJ, Eliassi-Rad B, Desai MA.** Ptosis after glaucoma surgery. Clin Ophthalmol. 2017;11:1483-1489.
15. **Takmaz T, Akmese HE, Onursever N.** Comparison of combined phacoemulsification-non-penetrating deep sclerectomy and phacoemulsification-trabeculectomy. International Eye Science. 2015;15(11):1851-1856.
16. **Tetz M, Koerber N, Shingleton BJ, et al.** Phacoemulsification and intraocular lens implantation before, during, or after canaloplasty in eyes with open-angle glaucoma: 3-year results. Journal of Glaucoma. 2015;24(3):187-194.
17. **Yadgarov A, Liu D, Crane ES, Khouri AS.** Surgical Outcomes of Ahmed or Baerveldt Tube Shunt Implantation for medically Uncontrolled Traumatic Glaucoma. J Curr Glaucoma Pract. 2017;11(1):16-21.
18. **Zvandasara T, Aazem M, Seemeen D, Turner J.** Viscocanalostomy/phacoviscocanalostomy, augmented with Nd: YAG laser goniopuncture for uncontrolled intraocular pressure: 1 year results. International Eye Science. 2014;14(2):195-201.

No Relevant Comparator:

19. **Ahuja Y, Ma Khin PS, Malihi M, Hodge DO, Sit AJ.** Clinical results of ab interno trabeculotomy using the trabectome for open-angle glaucoma: the Mayo Clinic series in Rochester, Minnesota. American Journal of Ophthalmology. 2013;156(5):927-935.
20. **Akil H, Chopra V, Huang AS, Swamy R, Francis BA.** Short-Term Clinical Results of Ab Interno Trabeculotomy Using the Trabectome with or without Cataract Surgery for Open-Angle Glaucoma Patients of High Intraocular Pressure. J Ophthalmol. 2017;2017:8248710.
21. **Akil H, Huang P, Chopra V, Francis B.** Assessment of Anterior Segment Measurements with Swept Source Optical Coherence Tomography before and after Ab Interno Trabeculotomy (Trabectome) Surgery. J Ophthalmol. 2016;2016:4861837.
22. **Bussel II, Kaplowitz K, Schuman JS, Loewen NA, Group TS.** Outcomes of ab interno trabeculectomy with the trabectome after failed trabeculectomy. British Journal of Ophthalmology. 2015;99(2):258-262.
23. **Bussel II, Kaplowitz K, Schuman JS, Loewen NA, Group TS**. Outcomes of ab interno trabeculectomy with the trabectome by degree of angle opening. British Journal of Ophthalmology. 2015;99(7):914-919.
24. **Dang Y, Roy P, Bussel II, Loewen RT, Parikh H, Loewen NA.** Combined analysis of trabectome and phaco-trabectome outcomes by glaucoma severity. F1000Res. 2016;5:762.
25. **Fea AM, Spinetta R, Cannizzo PML, et al.** Evaluation of Bleb Morphology and Reduction in IOP and Glaucoma Medication following Implantation of a Novel Gel Stent. J Ophthalmol. 2017;2017:9364910.
26. **Jordan JF, Wecker T, van Oterendorp C, et al.** Trabectome surgery for primary and secondary open angle glaucomas. Graefe's Archive for Clinical and Experimental Ophthalmology. 2013;251(12):2753-2760.
27. **Kahook MY, Lathrop KL, Noecker RJ.** One-site versus two-site endoscopic cyclophotocoagulation. Journal of Glaucoma. 2007;16(6):527-530.
28. **Klamann MK, Gonnermann J, Maier AK, Bertelmann E, Joussen AM, Torun N.** Influence of Selective Laser Trabeculoplasty (SLT) on combined clear cornea phacoemulsification and Trabectome outcomes. Graefe's Archive for Clinical and Experimental Ophthalmology. 2014;252(4):627-631.
29. **Klamann MK, Gonnermann J, Maier AK, et al.** Combined clear cornea phacoemulsification in the treatment of pseudoexfoliative glaucoma associated with cataract: significance of trabecular aspiration and ab interno trabeculectomy. Graefe's Archive for Clinical and Experimental Ophthalmology. 2013;251(9):2195-2199.
30. **Minckler D, Mosaed S, Dustin L, Ms BF, Group TS.** Trabectome (trabeculectomy-internal approach): additional experience and extended follow-up. Transactions of the American Ophthalmological Society. 2008;106:149-159.
31. **Neiweem AE, Bussel II, Schuman JS, Brown EN, Loewen NA.** Glaucoma Surgery Calculator: Limited Additive Effect of Phacoemulsification on Intraocular Pressure in Ab Interno Trabeculectomy. PLoS One. 2016;11(4):e0153585.
32. **Okeke CO, Miller-Ellis E, Rojas M, Trabectome Study Group.** Trabectome success factors. Medicine. 2017;96(24):e7061.
33. **Pahlitzsch M, Gonnermann J, Maier AB, Bertelmann E, Klamann MK, Erb C.** Modified goniotomy as an alternative to trabectome in primary open angle glaucoma and pseudoexfoliation glaucoma: 1 year results. Canadian Journal of Ophthalmology. 2017;52(1):92-98.
34. **Parikh HA, Bussel II, Schuman JS, Brown EN, Loewen NA.** Coarsened Exact Matching of Phaco-Trabectome to Trabectome in Phakic Patients: Lack of Additional Pressure Reduction from Phacoemulsification. PLoS One. 2016;11(2):e0149384.
35. **Patel I, de Klerk TA, Au L.** Manchester iStent study: early results from a prospective UK case series. Clinical & Experimental Ophthalmology. 2013;41(7):648-652.
36. **Sheybani A, Lenzhofer M, Hohensinn M, Reitsamer H, Ahmed II.** Phacoemulsification combined with a new ab interno gel stent to treat open-angle glaucoma: Pilot study. Journal of Cataract and Refractive Surgery. 2015;41(9):1905-1909.
37. **Shoji N, Kasahara M, Iijima A, et al.** Short-term evaluation of Trabectome surgery performed on Japanese patients with open-angle glaucoma. Jpn J Ophthalmol. 2016;60(3):156-165.
38. **Ting JL, Damji KF, Stiles MC, Group TS.** Ab interno trabeculectomy: outcomes in exfoliation versus primary open-angle glaucoma. Journal of Cataract and Refractive Surgery. 2012;38(2):315-323.
39. **Tojo N, Abe S, Hayashi A**. Factors That Influence of Trabectome Surgery for Glaucoma Patients. Journal of Glaucoma. 2017;26(9):835-844.

40. **Tojo N, Abe S, Miyakoshi M, Hayashi A.** Comparison of intraocular pressure fluctuations before and after ab interno trabeculectomy in pseudoexfoliation glaucoma patients. Clin Ophthalmol. 2017;11:1667-1675.

41. **Vold SD, Dustin L, Group TS.** Impact of laser trabeculoplasty on Trabectome outcomes. Ophthalmic Surgery, Lasers & Imaging. 2010;41(4):443-451.

42. **Widder,R.A.,Dinslage,S.,Rosentreter,A.,Jordan,J.F.,Kuhnrich,P.,Cursiefen,C.,Lemmen,K.-D.,Dietlein,T.S.**. A new surgical triple procedure in pseudoexfoliation glaucoma using cataract surgery, Trabectome, and trabecular aspiration. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2014///. 252:1971.

43. **Widder RA, Jordan JF, Kuhnrich P, Luebke J, Roessler GF, Anton A.** The effect of additional trabecular aspiration to phacoemulsification and trabectome as a triple procedure in pseudoexfoliation glaucoma: a case-matched study. International Ophthalmology. 2017.

No Relevant Outcome:

44. **Fea AM, Consolandi G, Pignata G, et al.** A comparison of endothelial cell loss in combined cataract and MIGS (Hydrus) procedure to phacoemulsification alone: 6-month results. J Ophthalmol. 2015;2015:769289.

45. **Wang JC, Campos-Moller X, Shah M, Sheybani A, Ahmed II.** Effect of endocyclophotocoagulation on refractive outcomes in angle-closure eyes after phacoemulsification and posterior chamber intraocular lens implantation. Journal of Cataract and Refractive Surgery. 2016;42(1):132-137.

Irrelevant Study Design:

46. **Gedde SJ, Kornmann HL.** Glaucoma surgery in pseudophakic eyes: Tube shunt first. Surv Ophthalmol. 2017;62(1):108-112.

47. **Masood I, Sigona M, Pajaujis M.** Re: Schlenker et al.: Efficacy, safety, and risk factors for failure of standalone ab interno gelatin microstent implantation versus standalone trabeculectomy (Ophthalmology. 2017;124:1579-1588). Ophthalmology. 2018;125(2):e16-17.

48. **Nugent R, Lee GA.** Glaucoma shunt oculodynia. Clin Exp Ophthalmol. 2017;45(8):836-837.

49. **Lindstrom RL.** Comprehensive ophthalmologists take combination approach to treating glaucoma. Ocular Surgery News. 2008;35(16):4-4.

50. **Shimizu A, Maruyama K, Yokoyama Y, Tsuda S, Ryu M, Nakazawa T.** Characteristics of uveitic glaucoma and evaluation of its surgical treatment. Clin Ophthalmol. 2014;8:2383-2389.

Other — Mixed Intervention and Comparator:

51. **Esfandiari H, Shazly T, Waxman S, et al.** Similar performance of trabectome and Ahmed glaucoma devices in a propensity score matched comparison. Journal of Glaucoma. 2018.

52. **Kostanyan T, Shazly T, Kaplowitz KB, et al.** Longer-term Baerveldt to Trabectome glaucoma surgery comparison using propensity score matching. Graefe's Archive for Clinical and Experimental Ophthalmology. 2017.

Appendix 7: Included Comparisons and Rationale Regarding Meta-Analyses — Clinical Review

Intervention	Comparator	Studies	Meta-Analysis Appropriate?
Research Questions 1 and 2			
MIGS Vs. Pharmacotherapy			
2x iStent	Travoprost (prostaglandin F analog)	Vold et al. 2016[58]	NO: Differences in the intervention (1st vs. 2nd generation iStent) and comparator (1 vs. 2 medications)
2x iStent Inject	Combination Latanoprost/timolol (prostaglandin F analog and beta-blocker)	Fea et al. 2014[36]	
MIGS Vs. Laser Therapy			
Hydrus Microstent	SLT	Fea et al. 2017[62]	NA
MIGS Vs. Another MIGS			
iStent vs. 2x iStent vs. 3x iStent	See column 1	Katz et al. 2018[59] and 2015[60]	NA
MIGS Vs. Filtration Surgery			
ECP	Second GDD-2 (BGI) or AGI	Murakami et al. 2017[63] Lima et al. 2004[61]	NO: Different study designs, differences in patient populations (e.g., ~15 mm Hg difference in baseline IOP), differences in comparators (BGI or AGI)
Trabectome or 2x iStent Inject (combined [MIGS] or separate in analyses)	Trabeculectomy with MMC	Pahlitzsch et al. 2017[25] Jea et al. 2012[64]	NO: Different study designs (retrospective cohort, NRS), differences in patient populations (cohorts ~10 y difference in age; type of OAG NR in one study, and variety of types in the other; previous ocular procedures NR in one study and ~25% of sample in the other; more systemic hypertension in one sample; baseline IOP different by ~6 mm Hg)
XEN 45 microstent with MMC	Trabeculectomy with MMC	Schlenker et al. 2017[65]	NA
Research Questions 3 and 4			
MIGS + Cataract Surgery Vs. Cataract Surgery Alone			
ECP + Phaco	Phaco alone	Kang et al. 2017[72] Perez Bartolome et al. 2017[73] Sheybani et al. 2015[74] Siegel et al. 2015[75] Francis et al. 2014 [84]	NO: Different study designs (retrospective vs. prospective cohorts); different follow-up durations (ranging from 2 to 36 mo)

Intervention	Comparator	Studies	Meta-Analysis Appropriate?
iStent + Phaco or 2x iStent + Phaco	Phaco alone	Fea et al. 2015[66] Fea 2010[67] Craven et al. 2012[68] Samuelson et al. 2011[34] El Wardani et al. 2015[76] Fernandez-Barrientos et al. 2010[69]	YES, subset: The two RCTs (Fea et al. 2015 and 2010; Craven et al. 2012 and Samuelson et al. 2011) were methodologically, statistically, and clinically suitable for pooling NO: El Wardani et al. was a different study design (retrospective cohort); Fernandez-Barrientos had a difference in intervention (2 iStents vs. 1 iStent)
CyPass Micro-Stent + Phaco[a]	Phaco alone	Vold et al. 2016[70]	NA
Hydrus Microstent	Phaco alone	Pfeiffer et al. 2015[71] Samuelson et al. 2018[88]	YES: These studies were methodologically, statistically, and clinically suitable for pooling
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery			
KDB + Phaco vs. iStent + Phaco	See column 1	Dorairaj et al. 2018[86]	NA
Trabectome + Phaco vs. 2x iStent + Phaco	See column 1	Kurji et al. 2017[79] Khan et al. 2015[78]	YES: These studies were methodologically, statistically, and clinically suitable for pooling
Trabectome + MICS vs. 2x iStent Inject + MICS	See column 1	Gonnermann et al. 2017[77]	NA
iStent + Phaco vs. 2x iStent + Phaco vs. 3x iStent + Phaco	See column 1	Vlasov and Kim 2017[80] Belovay et al. 2012[83]	NO: Different study designs (retrospective cohort vs. NRS), differences in intervention/comparison (different numbers of iStents)
ECP + iStent + Phaco	iStent + Phaco	Ferguson et al. 2017[81]	NA
ECP + Phaco vs. Trabectome + Phaco	See column 1	Moghimi et al. 2018[89]	NA
MIGS + Cataract Surgery Vs. Invasive Surgery + Cataract Surgery			
Trabectome + Phaco	Trabeculectomy with MMC + Phaco	Ting et al. 2018[87]	NA
Trabectome + Phaco	Trabeculotomy + Phaco	Kinoshita-Nakano et al. 2018[85]	NA
ECP + Phaco	Trabeculectomy with MMC + Phaco	Marco et al. 2017[82]	NA

2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; BGI = Baerveldt glaucoma implant 250 or 350; ECP = endoscopic cyclophotocoagulation; GDD = glaucoma drainage device; IOP = intraocular pressure; KDB = Kahook Dual Blade; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = months; NA = not applicable; NR = not reported; NRS = non-randomized intervention study; OAG = open-angle glaucoma; Phaco = phacoemulsification; RCT = randomized controlled trial; SLT = selective laser trabeculoplasty; vs. = versus; y = years.

[a] The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the Medical Devices Active Licence Listing and is therefore included in this report.

Appendix 8: Characteristics of Included Studies — Clinical Review

Table 28: Study Characteristics — Clinical Review

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
Research Questions 1 and 2					
MIGS Vs. Pharmacotherapy					
Vold et al. 2016[58] Armenia Funding source: Glaukos Corporation	RCT Analytical approach NR *Follow-up:* 1, 3, 6, 12, 18, 24, 30, and 36 mo *Loss to follow-up,* n (%)*:* At 12 mo: 2x iStent, 1 (2%); Travoprost, 0 (0%) At 24 mo: 2x iStent, 2 (4%); Travoprost, 1 (2%) At 36 mo: 2x iStent, 20 (37%); Travoprost, 14 (30%)	N = 101 eyes (101 patients) **Inclusion criteria:** Treatment-naive phakic patients with newly diagnosed POAG or PXF or ocular hypertension with IOP ≥ 21 mm Hg and ≤ 40 mm Hg, cup to disk ratio ≤ 0.9 and normal angle anatomy **Exclusion criteria:** Patients with uveitic, neovascular, or angle-closure glaucoma; glaucoma associated with vascular disorders; corneal pathology or prior surgery; congenital or traumatic cataract or prior cataract surgery; retinal or optic nerve disorders; ocular disease or condition that would place the participant at risk, confound study results or interfere with participation; participants in clinical trials; pregnant or nursing women	2x iStent Travoprost (medication; prostaglandin F analog, 0.004%)	**Clinical effectiveness:** IOP (Goldmann applanation tonometry), proportion of eyes with IOP ≤ 18 mm Hg or ≤ 15 mm Hg without additional medical therapy, BCVA (decimal chart), VF (Humphrey 24-2 SITA) **Safety:** Complications	1, 2
Fea et al. 2014[36] Italy, Spain, Poland, Germany,	RCT Between-group comparisons using Fisher's exact test	N = 192 eyes (192 patients) **Inclusion criteria:** Patients with OAG and a post-washout IOP	2x iStent Inject Latanoprost + Timolol (two medications; fixed combination	**Clinical effectiveness:** IOP (measured between 8 to 11 AM), proportion of patients who achieved an IOP reduction ≥	1, 2

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
UK, Armenia Funding source: Glaukos corporation	*Follow-up:* 1 d; 1, 3, 6, 9, and 12 mo *Loss to follow-up,* n (%)*:* At 12 mo, 2x iStent Inject, 0 (0%); Latanoprost + Timolol, 7 (8%)	between ≥ 22 mm Hg and < 38 mm Hg; BCVA of 20/200 or better; scleral spur clearly visibly by gonioscopy; able and willing to attend follow-up visits for 1 y; prior SLT not performed within 90 days of screening visit **Exclusion criteria:** Patients who were known non-responders to Latanoprost; had secondary glaucoma (except PXF and pigmentary); prior incisional glaucoma surgery or procedure (e.g., Trabeculectomy shunt or collagen implant); cloudy cornea inhibiting gonioscopic view; signs of traumatic or uveitic, neovascular, or angle-closure glaucoma	of Latanoprost/timolol; prostaglandin F analog and beta-blocker)	20%, ≥ 30%, ≥ 40%, or ≥ 50% versus unmedicated baseline IOP, proportion of patients who achieved an IOP ≤ 18 mm Hg or ≤15 mm Hg, BCVA **Safety:** Adverse events	
MIGS Vs. Laser Therapy					
Fea et al. 2017[62] Italy Funding source: None	Prospective cohort Within-group comparisons using two-sided paired t-tests; between-group differences using unpaired two-sided t-tests; prediction of primary outcomes (IOP and number of glaucoma medications at 12 mo) using linear regression	N = 56 eyes (56 patients) **Inclusion criteria:** Consecutive patients with POAG not sufficiently controlled by, intolerant of, or noncompliant with current IOP regimen; IOP > 21 mm Hg on at least two consecutive measurements; VF loss on Octopus or Humphrey automated perimetry and glaucomatous alterations to	Hydrus Microstent SLT	**Clinical effectiveness:** IOP (Goldmann applanation tonometry; median of at least 3 measurements in the week before treatment, NR for follow-up), number of glaucoma medications, VA **Safety:** Intraoperative complications, rate of adverse events, loss of VA and ocular health	1, 2

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
	Follow-up: 1 d; 1 wk; 1, 3, 6, and 12 mo *Loss to follow-up:* 1 patient (3%) in Hydrus group	optic nerve head **Exclusion criteria:** Eye surgery in previous 6 mo, any previous incisional glaucoma surgery, glaucoma type other than POAG, Shaffer angle grade of ≤ 2, medication with systemic or topical steroids			
MIGS Vs. Another MIGS					
Katz et al. 2018[59] and Katz et al. 2015[60] Armenia Funding source: Glaukos Corporation	RCT ITT and "modified ITT" (including subset of patients who did not undergo cataract surgery prior to 12 mo follow-up) analyses; between-group comparisons using Tukey's pairwise multiple-comparison test *Follow-up:* 1 d; 1 wk; 1, 3, 6, 12, 13, 18, 24, 25, 30, 36, 37, and 42 mo *Loss to follow-up,* n (%): At 12 and 18 mo: None At 42 mo: iStent, 5 (13%); 2x iStent, 3 (7%); 3x iStent, 2 (5%)	N = 119 eyes (119 patients) **Inclusion criteria:** Phakic or pseudophakic participants with OAG (including pigmentary and PXF), mild-to-moderate stage of neuropathy, normal angle anatomy, C:D ratio ≤ 0.9, current treatment with 1 to 3 medications, preoperative medicated IOP of 18 mm Hg to 30 mm Hg, and unmedicated (post-washout) IOP of 22 to 38 mm Hg; willingness to attend scheduled follow-up examinations for 5 y post-operatively **Exclusion criteria:** Pseudophakia with anterior-chamber IOL; peripheral anterior synechia, rubeosis, or other angle abnormalities that could impair proper stent placement; prior stent	iStent 2x iStent 3x iStent	**Clinical effectiveness:** Medicated and unmedicated IOP (Goldmann applanation tonometry); proportion of eyes achieving IOP reduction ≥ 20%, ≤ 18 mm Hg, or ≤ 15 mm Hg without medication; number of eyes on glaucoma medications; proportion of eyes with BCVA equal to or better than 20/40, 20/100, and 20/200, VF **Safety:** Intraoperative, perioperative and post-operative complications	1, 2

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
		implantation in study eye; traumatic, uveitic, neovascular, or angle-closure glaucoma; glaucoma associated with vascular disorders; functionally significant VF loss; prior incisional glaucoma surgery; prior SLT within 90 days of screening; prior ALT, iridectomy, or laser iridotomy; VF status at risk by washout period; unmedicated IOP expected to be > 38 mm Hg after washout period; active corneal inflammation or edema; clinically significant corneal dystrophy; corneal surgery of any type; corneal opacities; congenital or traumatic cataract; retinal or optic nerve disorders; elevated episcleral venous pressure; clinically significant sequelae from trauma; chronic ocular inflammatory disease; BCVA worse than 20/200; fellow eye in the trial; pregnant or nursing women			
MIGS Vs. Filtration Surgery					
ECP Vs. Glaucoma Drainage Device					
Murakami et al. 2017[63] US Funding source:	Retrospective cohort Within-group comparisons using Students t-test and Wilcoxon paired signed-rank test; between-group	N = 73 eyes (73 patients) **Inclusion criteria:** Pseudophakic eyes; open-angle, angle closure, or secondary glaucoma; had a	ECP Second GDD-2 (BGI 250 or 350)	**Clinical effectiveness:** IOP (Goldmann applanation tonometry; mean value of 2 measurements on 2 visits prior to surgery, NR for follow-up), number of glaucoma	1, 2

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
None declared	comparisons using Student's t-test, Mann-Whitney test, and Fisher exact test or; Wilcoxon's test, Sign's test, ANOVA, and Student's t-test *Follow-up:* 1, 3, 6, 12, 18, and 24 mo *Loss to follow-up,* n (%)*:* At 3 mo: ECP, 0 (0%); GDD-2, 1 (2%) At 6 mo: ECP, 2 (8%); GDD-2, 5 (10%) At 12 mo: ECP, 6 (24%); GDD-2, 18 (38%) At 24 mo: ECP, 14 (54%); GDD-2, 28 (58%)	failed initial tube shunt (BGI) surgery > 6 mo prior; inadequate IOP control (> 21 mm Hg) on 2 or more glaucoma medications, or IOP ≤ 21 mm Hg but above a predetermined target IOP (based on baseline IOP, severity of optic nerve or VF damage, or progression of visual loss), or intolerant of medical therapy or on an oral carbonic anhydrase inhibitor; VA better than light perception; minimum 2 y follow-up **Exclusion criteria:** Neovascular glaucoma, VA light perception or worse, prior ciliary body ablation, non-patent aqueous shunt without fluid drainage to plate		medications **Safety:** Complications, surgical interventions to manage complications	
Lima et al. 2004[61] Brazil Funding source: NR	Non-randomized controlled clinical trial Between-group comparisons using Wilcoxon signed-rank test, Sign's test; ANOVA, Student t-test *Follow-up:* 1 wk; 1, 2, 3, 4, 5, 6, 12, 18, and 24 mo	N = 68 eyes (68 patients) **Inclusion criteria:** Pseudophakic eyes with IOP ≥ 35 mm Hg on maximum tolerated therapy, with at least 1 previous Trabeculectomy with antimetabolite, and a VA better than LP	ECP AGI	**Clinical effectiveness:** IOP (Goldmann tonometer, assessed around 10:00 AM in triplicate, but whether values were averaged or a single value was reported was NR); success (IOP > 6 mm Hg and < 21 mm Hg at 24 mo follow-up, with or without medication); number of medications; VA (LogMAR)	1, 2

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
	Mean follow-up ± SD: *ECP*, 21.29 ± 6.42 mo (range 2 to 24 mo) AGI, 19.82 ± 8.35 mo (range 2 to 24 mo) *P* = 0.4 *Loss to follow-up:* At 12 mo: ECP, 3 (8.8%); AGI, 7 (20.6%) At 24 mo: ECP, 6 (17.6%); AGI, 8 (23.5%)	**Exclusion criteria:** Previous glaucoma drainage device implantation or a cyclodestructive procedure, eyes that did not perceive light, eyes that had a retinal or choroidal detachment, or eyes with a failed corneal graft		**Safety:** Complications	
Trabectome (or 2x iStent Inject) Vs. Trabeculectomy					
Pahlitzsch et al. 2017[25] Germany Funding source: None	Prospective cohort Within-group comparisons using independent sample t-test; between two-group and three-group comparisons using Mann-Whitney U test and Kruskal-Wallis test respectively *Follow-up:* 1 d; 6 wk; 3 and 6 mo *Loss to follow-up:* None	N = 88 eyes (88 patients) **Inclusion criteria:** OAG, BCVA of at least 20/200 with reliable VF testing, age 50 to 90 y **Exclusion criteria:** Active inflammation in anterior/posterior chamber or a corneal infection; higher spherical errors or astigmatism; hazy optic media; ocular trauma; intraocular surgery or use of contact lenses within 3 mo; cancer, uncontrolled diabetes or hypertension, pulmonal disorders, metabolic syndromes, thyroid disorders	Trabectome or 2x iStent Inject (combined [MIGS] or separate in analyses) Trabeculectomy with MMC	**Clinical effectiveness:** QoL (12 subscales [general health, ocular pain, general vision, near activities, distance activities, mental health, social functioning, role difficulties, dependency, driving, colour vision, peripheral vision] and overall composite that included all but the general health parameter; NEI VFQ-25), IOP (Goldmann applanation tonometry), number of glaucoma medications, VA **Safety:** None	1

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
Jea et al. 2012[64] US Funding source: None	Retrospective cohort Between-group comparisons using Student t-test and chi-square tests *Follow-up:* 1, 3, 6, 12, 18, 24, and 30 mo *Mean follow-up ± SD:* Trabectome, 27.3 ± 15.4 mo (range, 2.1 to 62.6) Trabeculectomy, 25.5 ± 17.1 months (range, 2.3 to 61.4) *P* = 0.406 *Loss to follow-up,* n (%)*:* At 6 mo: Trabectome, 13 (11.3%); Trabeculectomy, 14 (13.7%) At 12 mo: Trabectome, 26 (22.6%); Trabeculectomy, 29 (28.4%) At 24 mo: Trabectome, 31 (27.0%); Trabeculectomy, 53 (52.0%) At 30 mo: Trabectome, 39 (33.9%); Trabeculectomy, 59 (57.8%)	N = 217 eyes (217 patients) **Inclusion criteria:** Consecutive patients; age ≥ 40 y, OAG (POAG, PXF, pigmentary glaucoma, or uveitic glaucoma provided that no peripheral anterior synechia were present) uncontrolled with maximum tolerable medical therapy **Exclusion criteria:** Concurrent surgical procedure (including cataract extraction)	Trabectome Trabeculectomy with MMC	**Clinical effectiveness:** IOP (mean of 2 visits at baseline; NR for follow-up), number of glaucoma medications, VA **Safety:** Complications, need for additional glaucoma procedures and surgeries	1, 2

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
Xen45 With MMC Vs. Trabeculectomy With MMC					
Schlenker et al. 2017[65] Austria, Belgium, Canada, Germany Funding source: None	Retrospective cohort Between-group comparisons using Fisher exact tests, 2-sided Student t-tests, or Wilcoxon tests *Follow-up:* median irrespective of censoring, Xen45, 15.0 mo (IQR 9.5 to 19.6); Trabeculectomy, 17.8 mo (IQR 12.6 to 25.4) *Loss to follow-up:* NR	N = 354 eyes (293 patients) **Inclusion criteria:** Consecutive patients; age 30 to 90 y with POAG, PXF, pigment dispersion, normal-tension, angle-recession, combined mechanism, history of angle-closure, or juvenile glaucoma, with above-target IOP on maximal medical therapy **Exclusion criteria:** Prior incisional filtering surgery; neovascular or uveitic glaucoma, iridocorneal endothelial syndrome or Axenfeld-Rieger syndrome; fibrous or epithelial downgrowth; previous corneal graft or retinal surgery; <1 mo follow-up	XEN 45 microstent with MMC (Xen45) Trabeculectomy with MMC	**Clinical effectiveness:** IOP, number of medications, BCVA (Snellen converted to logMAR) **Safety:** Post-operative interventions, reoperations, or complications	1, 2
Research Questions 3 and 4					
MIGS + Cataract Surgery Vs. Cataract Surgery Alone					
ECP + Phaco Vs. Phaco Alone					
Kang et al. 2017[72] UK Funding source: NR	Retrospective cohort Between-group comparisons using unpaired t-tests *Mean follow-up:* 21 mo (range 2 wk to 6 y 2 mo)	N = 124 eyes (114 patients) **Inclusion criteria:** Consecutive OAG (normal tension, PXF, pigmentary) patients with complete data	ECP + Phaco Phaco alone	**Clinical effectiveness:** IOP (Goldmann applanation tonometry), number of glaucoma medications, VA (Snellen VA)	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
	Loss to follow-up (ECP + Phaco group): 1 eye (< 1%); 40 eyes excluded due to incomplete data, unreliable measures, or incorrect intervention	**Exclusion criteria:** Missing follow-up data, VA of counting fingers or worse		**Safety:** Complications	
Perez Bartolome et al. 2017[73] UK Funding source: None	Retrospective cohort Between-group comparisons using Chi-squared test, Fisher exact test, and Student t-tests; within-group comparisons using paired t-tests *Follow-up:* 1 d; 1 wk; 1, 3, 6 mo; 1 y *Loss to follow-up,* n (%)*:* ECP + Phaco, 3 (4%); Phaco, 2 (6%) (from original sample of N = 104)	N = 99 eyes (99 patients) **Inclusion criteria:** Consecutive patients with POAG and cataract ECP + Phaco group: Uncontrolled glaucoma or previous failed glaucoma surgery (Trabeculectomy, GDD, transscleral cyclophotocoagulation) with ≥ 3 glaucoma medications or if fewer medications due to intolerance, at least 1 y follow-up Phaco alone: Early-stage glaucoma controlled with 1 to 2 medications **Exclusion criteria:** None	ECP + Phaco Phaco alone	**Clinical effectiveness:** IOP (Goldmann applanation tonometry), number of glaucoma medications, VA (Snellen converted to logarithm of the minimum angle of resolution) **Safety:** Post-operative complications	3, 4
Sheybani et al. 2015[74] US Funding source: NR	Retrospective cohort Between-group comparisons using Student t-test, Chi-squared test, and Fisher's exact tests; within-group comparisons using paired t-tests	N = 141 eyes (141 patients) **Inclusion criteria:** Consecutive patients with OAG, age 50 to 90 y **Exclusion criteria:** Patients with: advanced glaucomatous disease as determined by VF	ECP + Phaco Phaco alone	**Clinical effectiveness:** IOP (Goldmann applanation tonometry; averaged over 2-3 consecutive visits if available, otherwise a single value reported), number of glaucoma medications, BCVA (Snellen eye chart converted to logMAR)	3

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
	Follow-up, mean: ECP + Phaco, 7.4 mo; Phaco, 2.1 mo P < 0.05 *Loss to follow-up:* NA due to study design	(MD worse than –12.00 dB, defects affecting fixation); non-glaucomatous ocular disease with best-corrected vision before cataract formation of < 20/80; any prior ocular surgery; history of PXF, traumatic or uveitic glaucoma; uncontrolled diabetes; used oral carbonic anhydrase inhibitors; pregnant; intraoperative complications (e.g., anterior or posterior capsular tears, vitreous loss); required iris expansion, capsular staining, or corneal suture during surgery; lens implant not placed in the capsular bag (or with optic capture)		**Safety:** None	
Siegel et al. 2015[75] US Funding source: None	Retrospective cohort Between-group comparisons using unpaired t-tests, Mann-Whitney U test, repeated measures ANOVA *Follow-up:* 1, 6, 12, 18, 24, 30, and 36 mo *Loss to follow-up:* NR; possible that there were none lost to follow-up due to study design but this was not explicit	N = 313 eyes (161 patients) **Inclusion criteria:** Mild-to-moderate glaucoma (≥ 1 but < 3 glaucoma medications with defined but stable minimal glaucomatous field loss and cupping > 0.6 but < 0.8), well-controlled medically **Exclusion criteria:** Severe glaucoma; prior Phaco, cyclodestructive, filtering or other tube shunt procedures	ECP + Phaco Phaco alone	**Clinical effectiveness:** IOP, number of glaucoma medications, VA (Snellen) **Safety:** IOP spikes (acute rise in IOP > 10 mm Hg from preoperative baseline during the early post-operative period), surgical complications	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
Francis et al. 2014[84] US Funding source: NR	Prospective cohort Between-group comparisons using independent samples t-test, Wilcoxon rank sum test, and Chi-square test; within-group comparisons using paired t-test *Follow-up:* 6, 12, 24, and 36 mo *Loss to follow-up,* n (%)*:* At 6 mo: ECP + Phaco, 2 (2.5%); Phaco, 0 (0%) At 12 mo: ECP + Phaco, 1 (1.3%); Phaco, 0 (0%) At 24 mo: ECP + Phaco, 0 (0%); Phaco, 0 (0%) At 36 mo: ECP + Phaco, 35 (43.8%); Phaco, 37 (46.3%)	N = 160 eyes (160 patients) **Inclusion criteria:** Consecutive patients with medically controlled POAG with mild-to-moderate optic nerve damage with or without VF damage (mean deviation 0 to12 dB, without reduction in a paracentral point to below 10 dB); optic nerve damage characteristic of glaucoma, such as focal notching or an increase in generalized cupping from baseline; IOP ≥ 21 mm Hg **Exclusion criteria:** Patients without evidence of optic nerve damage; advanced uncontrolled glaucoma characterized by advanced optic nerve cupping and VF damage; glaucoma other than open-angle; previous filtration, tube, or cyclodestructive surgery; fewer than 6 months of follow-up due to dropout or insufficient time since surgery	ECP + Phaco Phaco alone	**Clinical effectiveness:** IOP, number of glaucoma medications **Safety:** Post-operative complications	3, 4
1 or 2 iStent(s) + Phaco Vs. Phaco Alone					
El Wardani et al. 2015[76] Switzerland Funding source:	Retrospective cohort Analytical approach NR *Follow-up:* 1, 3, and 6 wk; 3 and 6 mo	N = 131 eyes (105 patients) **Inclusion criteria:** Consecutive patients with cataract and ocular hypertension or mild/moderate primary	iStent + Phaco 2x iStent + Phaco Phaco alone	**Clinical effectiveness:** IOP, number of glaucoma medications, VA **Safety:** None	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
NR	*Loss to follow-up,* n (%)*:* At 6 mo: iStent + Phaco, 8 (26%); 2x iStent + Phaco, 5 (23%); Phaco alone, 32 (41%)	glaucoma (including PXF or pigmentary) or mixed-type glaucomas, with at least 1 glaucoma medication **Exclusion criteria:** Severely uncontrolled IOP, advanced glaucoma field defects, previous glaucoma surgery or corneal opacity preventing gonioscopic view of the iridocorneal angle			
Fea et al. 2015[66] and Fea 2010[67] Italy Funding source: NR	RCT Within-group comparisons using paired-sample t-tests; between-group comparisons using 2-sample t-tests or Fisher exact tests *Follow-up:* 1 d; 1 wk; 1, 2, 3, 6, 9, 12, and 15 mo; 4 y *Loss to follow-up,* n (%)*:* At 15 mo: iStent + Phaco, 0 (0%); Phaco, 3 (12.5%) At 4 y: iStent + Phaco, 2 (16.7%); Phaco, 10 (41.7%)	N = 36 eyes (36 patients) **Inclusion criteria:** POAG with IOP >18 mm Hg at 3 separate visits on ≥ 1 ocular hypotensive medications, preoperative corrected-distance VA no better than 0.6 (20/80), likely to follow surgeon instructions **Exclusion criteria:** Other glaucoma diagnosis, peripheral anterior synechias, a cloudy cornea likely to inhibit gonioscopic view of the angle, previous ocular surgery (including glaucoma-filtering surgery), history of trauma or ocular surface disease, pre-proliferative or proliferative diabetic retinopathy, age-related macular degeneration with macular scar or large macular atrophy that would inhibit potential VA	iStent + Phaco Phaco alone	**Clinical effectiveness:** IOP (medicated and unmedicated; Goldmann applanation tonometry), number of medications **Safety:** Adverse events	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
Craven et al. 2012[68] and Samuelson et al. 2011[34] US Funding source: Glaukos Corporation	RCT Between-group comparisons using 2-sample t-test, 2-sample or 1-sided z tests, and Fisher exact tests *Follow-up:* 1 d; 1-2 wk; 3, 6, 12, 18, and 24 mo *Loss to follow-up,* n (%)*:* At 12 mo: iStent + Phaco, 11 (9.4%); Phaco alone, 11 (8.9%) At 24 mo: iStent + Phaco, 19 (16.2%); Phaco alone, 22 (17.9%) At 24 mo: Analyses conducted as ITT (all randomized eyes) with last observation carried-forward approach, or with the "consistent cohort" (defined as eyes with IOP and ocular hypotensive medication data at screening, 12 mo, and 24 mo who did not have secondary surgical intervention that may confound the results)	N = 240 eyes (239 patients) **Inclusion criteria:** Mild-to-moderate OAG (including VF defects and/or optic nerve pathology, and C:D ≤ 0.8); IOP of ≤ 24 mm Hg while taking 1 to 3 medications; and unmedicated IOP ≥ 22 mm Hg and ≤ 36 mm Hg during normal office hours; clinically significant cataract with BCVA of 20/40 or worse in the presence of glare **Exclusion criteria:** Angle-closure glaucoma; neovascular, uveitic, or angle-recession glaucoma; secondary glaucoma (except PXF and pigmentary); severely uncontrolled IOP; severe glaucomatous field defects; previous glaucoma surgery (except iridectomy); previous refractive procedures; known corticosteroid responders; ocular disease that would affect safety; monocular patients or patients with a CDVA or BCVA worse than 20/200 in the fellow eye	iStent + Phaco Phaco alone	**Clinical effectiveness:** IOP (2-person applanation tonometry), number of medications, CDVA, VF (Humphrey 30-2 or 24-2 SITA standard) **Safety:** Complications and adverse events	3, 4
Fernandez-Barrientos et al. 2010[69]	RCT Between-group comparisons using Mann-Whitney	N = 33 eyes (33 patients) **Inclusion criteria:** Age ≥ 18 y; IOP > 17 and	2x iStent + Phaco Phaco alone	**Clinical effectiveness:** IOP (Goldmann applanation tonometry), number of medications	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
Spain Funding source: Glaukos Corporation	nonparametric test, Chi-square test, repeated measures analysis of variance (MANOVA), Friedman test *Follow-up:* 1 d 1 wk; 1-2 wk, 1, 3, 6, and 12 mo *Loss to follow-up:* None	< 31 mm Hg with treatment and > 21 mm Hg and <36 mm Hg after the pharmacologic washout period; cataract that requires surgery; scleral spur clearly visible with gonioscopy; has not undergone glaucoma incisional surgery or a laser procedure; minimum VA of 20/200 or better **Exclusion criteria:** Closed-angle glaucoma, secondary glaucoma, non-neovascular, uveitic, or angular recession glaucoma; previous glaucoma procedures (e.g., Trabeculectomy, viscocanalostomy, ALT, SLT, drainage implant, collagen implant, cyclodestruction procedure); threat of visual field fixation; cornea with opacity that impedes gonioscopy vision from the nasal angle; elevated episcleral venous pressure due to a history of thyroid orbitopathy, carotid cavernous fistula, orbital tumour, or congestive orbital illness; retrobulbar tumour; thyroid ocular illness; Sturge-Weber syndrome; chronic inflammatory disease; previous ocular trauma; peripheral anterior		**Safety:** Intraoperative complications	

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
		synechiae in the area where the implant is inserted; glaucoma due to vascular disorder; ocular surface disorders; glaucoma due to burns with chemical elements; previous refractive surgery that makes IOP measures difficult (PRK, RK, LASIK, LASEK)			
Hydrus Microstent + Phaco Vs. Phaco Alone					
Samuelson et al. 2018[88] Canada, Germany, Italy, Mexico, Philippines, Poland, Spain, UK, US Funding source: None	RCT Between- and within-group comparisons using 2-sample t-tests or the Fisher exact test *Follow-up:* 1, 3, 6, 12, 18, and 24 mo *Loss to follow-up,* n (%): Complete sample: 28 (5%) lost to 24-mo follow-up	N = 556 eyes (556 patients) **Inclusion criteria:** Age-related cataract; diagnosis of mild-to-moderate POAG on 1 to 4 topical glaucoma medications; ophthalmoscopically visible glaucomatous optic neuropathy, mild-to-moderate VF loss (Hodapp-Anderson-Parrish criteria), BCVA 20/40 or worse with or without brightness acuity testing, Schaffer grade III-IV angle in all 4 quadrants; medicated IOP ≤ 31 mm Hg; unmedicated modified DIOP between 22 mm Hg and 34 mm Hg with an increase of at least 3 mm Hg compared with medicated value; prior SLT was allowed **Exclusion criteria:** Cataract surgery complications; angle closure or any secondary	Hydrus Microstent + Phaco Phaco alone	**Clinical effectiveness:** Modified unmedicated DIOP (2-person Goldmann applanation tonometry; average of 3 measurements taken 4 ± 1 hours apart between 8 a.m. and 4 p.m.); IOP (2-person Goldmann applanation tonometry); proportion of eyes with unmedicated modified DIOP reduction of ≥ 20%, ≥ 30%, or ≥ 40% compared with baseline; number of medications **Safety:** Intraoperative complications, adverse events	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
		glaucoma; VF mean deviation between 0 and -12 dB; exudative ARMD; proliferative diabetic retinopathy; significant risk of glaucomatous progression with medication washout; narrow anterior-chamber angle (Shaffer grade I-II) or other angle abnormality; central corneal thickness < 480 µm or > 620 µm or clinically significant corneal dystrophy; prior corneal surgery, cycloablation, or any incisional glaucoma procedure (e.g., Trabeculectomy, tube shunt, deep sclerectomy, canaloplasty); prior ALT			
Pfeiffer et al. 2015[71] Germany, Italy, Spain, The Netherlands Funding source: Ivantis, Inc. and the University Medical Center Mainz (Mainz, Germany)	RCT Within-group and between-group comparisons using unpaired t-tests or the Fisher exact test *Follow-up:* 1 d; 1 wk; 1, 3, 6, 12, 18, and 24 mo *Loss to follow-up,* n (%)*:* At 12 mo: Hydrus + Phaco, 2 (4%); Phaco, 1 (2%) At 24 mo: Hydrus + Phaco, 3 (6%);	N = 100 eyes (100 patients) **Inclusion criteria:** Patients with OAG and cataract; IOP ≤ 24 mm Hg with no more than 4 hypotensive medications; DIOP between 21 mm Hg and 36 mm Hg; Shaffer grade III or IV chamber angle in all quadrants, HVF changes characteristic of glaucoma or glaucomatous optic nerve damage confirmed by ophthalmoscopy and nerve fibre layer imaging; ability to safely undergo medication washout	Hydrus Microstent (Hydrus) + Phaco Phaco alone	**Clinical effectiveness:** DIOP (unmedicated; 2-person Goldmann applanation tonometry, average of: mean of duplicate or median of triplicate measures taken at 3 time points 4 h apart between 8 a.m. and 4 p.m.), proportion of eyes with ≥ 20% reduction in washed-out DIOP, number of medications **Safety:** Complications, adverse events	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
	Phaco, 7 (4%) *Patients lost to follow-up and/or without medication washout at follow-up (i.e., non-evaluable),* n (%): At 12 mo: Hydrus + Phaco, 6 (12%); Phaco, 16 (32%)	**Exclusion criteria:** Angle-closure glaucoma; secondary glaucomas (except PXF or pigment dispersion glaucomas); exudative age-related macular degeneration; proliferative diabetic retinopathy; significant risk of vision loss because of washout of IOP-lowering medications; narrow angle or other angle abnormality visible on gonioscopy; central corneal thickness < 480 µm or > 620 µm; clinically significant corneal dystrophy; prior eye procedures (corneal surgery, ALT, cycloablation, any incisional glaucoma procedure such as Trabeculectomy, tube shunts, deep sclerectomy, canaloplasty)			
Other Comparisons (From Single Studies)					
Vold et al. 2016[70] US Funding source: "NA"	RCT Comparisons using Fisher exact test and Student t-test, using per-protocol and intention-to-treat analyses *Follow-up:* 1 and 7 d; 1, 3, 6, 12, 18 and 24 mo *Loss to follow-up*, n (%)*:* 25 (5.0%) lost to 24-mo follow-up, and additional 32 (6.3%)	N = 505 eyes (505 patients) **Inclusion criteria:** Age ≥ 45 y with POAG; screening medicated IOP ≤ 25 mm Hg or unmedicated between 21 mm Hg and 33 mm Hg; baseline unmedicated diurnal IOP between 21 mm Hg and 33 mm Hg and ≥ 3 mm Hg greater than screening IOP; age-related cataract with BCVA or acuity testing of 20/40 or worse	CyPass Micro-Stent + Phaco Phaco alone Note: The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from this study;[37,38] however, at the time of report publication, this device was still active in the MDALL and is therefore included in this	**Clinical effectiveness:** IOP (2-person Goldmann applanation tonometry; means of 2 measurements determined at approx. 8 a.m., noon, and 4 p.m. were averaged to provide mean DIOP at baseline, NR for follow-up), proportion of eyes with unmedicated IOP of 6 mm Hg to 18 mm Hg, number of medications **Safety:** Adverse events	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
	followed-up but not per-protocol	eligible for Phaco with IOL implantation **Exclusion criteria:** > 3 ocular hypotensive medications; significant risk with medication washout; previous corneal or glaucoma surgery (except laser trabeculoplasty); other clinically significant ocular pathology; diagnosis of acute angle closure or traumatic, congenital, malignant, uveitic, PXF, pigmentary, or neovascular glaucoma	report.		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery					
Goniotomy With Kahook Dual Blade + Phaco Vs. iStent + Phaco					
Dorairaj et al. 2018[86] US and Mexico Funding source: None	Retrospective cohort Between-group comparisons using mixed model techniques with Bonferroni's method to address multiple comparisons *Follow-up:* 1 d; 1 wk; 1, 3 and 6 mo *Loss to follow-up*, n (%): At 1 mo: KDB + Phaco, 14 (5.9%); iStent + Phaco, 35 (17.7%) At 3 mo: KDB + Phaco, 34 (14.3%); iStent + Phaco, 70 (35.4%)	N = 435 eyes (318 patients) **Inclusion criteria:** Patients aged 18 to 89 years diagnosed with mild-to-moderate glaucoma (defined by International Classification of Diseases 9 definitions); IOP controlled with ≥ 1 topical medications; having undergone uncomplicated Phaco and posterior chamber IOL implantation with goniotomy using the KDB or implantation of a single iStent; with complete follow-up data **Exclusion criteria:** Ocular comorbidities reducing BCDVA;	Goniotomy with the KDB + Phaco (KDB + Phaco) iStent + Phaco	**Clinical effectiveness:** IOP (Goldmann applanation tonometry), proportion of patients with IOP reduction of ≥ 20% from baseline, number of medications, BCVA (Snellen acuity chart at 20 foot equivalent distance under mesopic lighting converted to logMAR) **Safety:** Adverse events, secondary surgical interventions	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
	At 6 mo: NA due to study design	cataract surgery complicated by vitreous loss, vitrectomy, or IOL implantation in the sulcus or anterior chamber; prior incisional glaucoma surgery			
Trabectome + Phaco Vs. 2x iStent + Phaco					
Kurji et al. 2017[79] Canada Funding source: NR	Retrospective cohort Between-group comparisons at baseline using Wilcoxon rank sums and Chi-square test; between-group comparisons from baseline to follow-up using generalized estimating equation to control for correlation between eyes for patients with more than 1 eye enrolled in the study; prediction of primary outcome (IOP at 6 and 12 mo) using multivariate regression *Follow-up:* 1 d; 1 wk; 1, 3, 6 and 12 mo *Loss to follow-up,* n (%): 6 (9%) patients (3 in each group)	N = 70 eyes (55 patients) **Inclusion criteria:** Consecutive patients; age 18 to 85 y; early, moderate, or advanced OAG (including PXF) with open angles; IOP ≥ 18 mm Hg on at least one glaucoma medication; 12 mo follow-up; prior SLT or ALT were acceptable **Exclusion criteria:** angle-closure glaucoma, cornea edema, ocular problems precluding accurate tonometry, absence of clear angle landmarks, peripheral anterior synechiae, increased episcleral venous pressure, evidence of other ocular disease, prior angle or filtering procedure, history of refractive surgery or ocular trauma, use of steroids concurrently or within previous 3 mo, presence of significant health conditions (e.g., uncontrolled diabetes)	Trabectome + Phaco 2x iStent + Phaco	**Clinical effectiveness:** IOP (Goldman applanation tonometer), number of glaucoma medications, BCVA (Snellen) **Safety:** Complications	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
Khan et al. 2015[78] Canada and US Funding source: None	Retrospective cohort Within-group comparisons using Wilcoxon signed-rank test; between-group comparisons using Fisher exact test, Student t-test, and Mann-Whitney U test; changes in IOP across time (baseline to 12 mo) and between groups assessed using 2-way ANOVA *Follow-up:* 1 d; 1 wk; 1, 3, 6 and 12 mo *Loss to follow-up,* n (%)*:* At 6 mo: Trabectome + Phaco, 5 (9.6%); 2x iStent + Phaco, 8 (16.3%) At 12 mo: NR; analyses conducted with last observation carried forward (with the complete sample)	N = 101 eyes (101 patients) **Inclusion criteria:** POAG, PXF, or pigmentary dispersion glaucoma of any severity **Exclusion criteria:** Patients with adjunctive surgery such as ECP, endocycloplasty, or goniosynechialysis; angle-closure glaucoma; previous incisional conjunctival surgery; post-operative follow-up less than 12 mo	Trabectome + Phaco 2x iStent + Phaco	**Clinical effectiveness:** IOP, number of medications **Safety:** Post-operative adverse events	3, 4
Trabectome + MICS Vs. iStent/iStent Inject + MICS					
Gonnermann et al. 2017[77] Germany Funding source: None	Retrospective cohort Between-group comparisons (intra-individual eye comparison) using student's t-test, or the Mann-Whitney U or Wilcoxon-Rank-signed-test *Follow-up:* 1 d; 6 wk; 3, 6, and 12 mo	N = 50 eyes (25 patients) **Inclusion criteria:** IOP above target with worsening glaucoma on maximally tolerated medical treatment; mild/moderate VF defects **Exclusion criteria:** Previous surgery or laser treatment; other	Trabectome + MICS 2 iStent Inject + MICS	**Clinical effectiveness:** IOP (Goldmann applanation tonometry), number of glaucoma medications, BCVA **Safety:** Number of post-operative interventions, complications	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
	Loss to follow-up: 2 eyes (7%) in each group (required Trabeculectomy) from original sample size of n = 27 per group	ocular or systemic diseases; missing follow-up exams			
Different Numbers of iStents + Phaco					
Vlasov and Kim 2017[80] US Funding source: NR	Retrospective cohort Between-group comparisons using paired-sample t-tests; within-group comparisons using Wilcoxon signed-rank tests *Follow-up:* 1 d; 1 wk; 1, 3, 6, and 12 mo *Loss to follow-up,* n (%)*:* *A*t 12 mo: iStent + Phaco, 11 (28%); 2x iStent + Phaco, 17 (57%)	N = 69 eyes (69 patients) **Inclusion criteria:** Patients with POAG, PXF, or pigmentary dispersion glaucoma at any stage of severity and with visually significant cataract **Exclusion criteria:** None	iStent + Phaco 2x iStent + Phaco	**Clinical effectiveness:** IOP, number of medications **Safety:** Complications or adverse events	3, 4
Belovay et al. 2012[83] Canada Funding source: NR	Non-randomized controlled clinical trial Within-group comparisons using paired t-test; between-group comparisons using 2 sample t-test, Mann-Whitney test, Fisher exact test *Follow-up:* 1 d; 1 wk; 1, 3, 6, and 12 mo *Loss to follow-up:* NA due to study design	N = 53 eyes (47 patients) **Inclusion criteria:** Visually significant cataract, IOP that was not well-controlled on medication or was well-controlled but ≥ 3 medications, 12 mo follow-up **Exclusion criteria:** None	2x iStent + Phaco 3x iStent + Phaco	**Clinical effectiveness:** IOP (Goldmann applanation tonometry), proportion of patients with IOP ≤ 15 mm Hg at 12 mo, number of medications, CDVA (Snellen) **Safety:** Complications	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
ECP + iStent + Phaco Vs. iStent + Phaco					
Ferguson et al. 2017[81] US Funding source: NR	Retrospective cohort Within-group comparisons using paired t-test or Wilcoxon signed-rank test; between-group comparisons using independent sample t-tests and Wilcoxon Mann-Whitney test *Follow-up:* 1 d; 1 wk; 1, 3, 6, and 12 mo *Loss to follow-up,* n (%): At 12 mo: ECP + iStent + Phaco, 3(6%); iStent + Phaco, 0 (0%)	N = 101 eyes (76 patients) **Inclusion criteria:** Consecutive patients with mild, moderate, or severe OAG; 1 or more medications at baseline **Exclusion criteria:** None	ECP + iStent + Phaco iStent + Phaco	**Clinical effectiveness:** IOP (Goldmann applanation tonometry), number of glaucoma medications **Safety:** Need for additional surgery, post-operative complications, IOP increases of >15 mm Hg	3, 4
ECP + Phaco Vs. Trabectome + Phaco					
Moghimi et al. 2018[89] Iran Funding source: None	Retrospective cohort Between-group comparisons using Kruskal-Wallis test, Chi-squared, or Fisher exact test; within-group comparisons using Wilcoxon signed-rank test *Follow-up:* 1 d; 1 wk; 1, 3, 6, 12 and 24 mo Mean follow-up, complete sample: 17.2 ± 5.5 mo (range 12 to 24 mo) *Loss to follow-up:* NA due to study design	N = 61 eyes (61 patients) **Inclusion criteria:** Patients with age > 40 y; OAG (defined by glaucomatous optic disc damage with or without VF damage) and visually significant cataract; IOP < 30 mm Hg with or without glaucoma medication; treated with ECP + Phaco or Trabectome + Phaco (or phacoviscocanalostomy — excluded from the present report) and with at least 12 mo follow-up	ECP + Phaco Trabectome + Phaco	**Clinical effectiveness:** IOP (Goldmann applanation tonometer), number of medications, visual field (static automated white-on-white threshold perimetry program 24-2, SITA standard) **Safety:** Complications	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
		Exclusion criteria: Patients with secondary angle-closure glaucoma or neovascular glaucoma, history of surgery or trauma to the enrolled eye			
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery					
Ting et al. 2018[87] Canada Funding source: University of Alberta, Faculty of Medicine and Dentistry	RCT Within-group comparisons using a general linear mixed model; between-group comparisons using Chi-squared test, Fisher's exact test, or Wilcoxon rank sum *Follow-up:* 6 and 12 mo *Loss to follow-up,* n (%): At 6 and 12 mo: Trabectome + Phaco, 1 (10%); Trabeculectomy + Phaco, 1 (11%)	N = 19 eyes (19 patients) **Inclusion criteria:** Age 40 to 85 y; OAG (≥ Shaffer Grade 2); inadequately controlled glaucoma and/or IOP on tolerated medical therapy; visually significant cataract (opacification of the crystalline lens with attributable reduction in BCVA to ≤ 20/30); availability for at least 1 y follow-up **Exclusion criteria:** angle-closure glaucoma; secondary OAG (with the exception of PSF glaucoma); absence of clear angle landmarks on gonioscopy; other ocular disease affecting assessments of VA, VF, or tonometry; prior angle or filtering surgery; steroid use within the past 3 mo	Trabectome + Phaco Trabeculectomy with MMC + Phaco	**Clinical effectiveness:** IOP (Goldmann applanation tonometry; mean of 2 consecutive measurements or median of 3 if the first 2 were not within 2 mm Hg); number of medications **Safety:** Surgical complications (early [≤3 0 d post-operative] or late [> 30 d post-operative]; mild, moderate, or severe), secondary glaucoma surgery	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
Kinoshita-Nakano et al. 2018[85] Japan Funding source: The Japan Society for the Promotion of Science KAKENHI Grant	Prospective and retrospective cohort Data for Trabectome + Phaco group were collected prospectively; data for Trabeculotomy + Phaco group were collected retrospectively Between-group comparisons using Mann-Whitney U tests or Chi-squared tests *Follow-up:* 3, 6, 12, 18, 24, and 36 mo *Loss to follow-up,* n (%): At 12 mo: Trabectome + Phaco, 3 (6%); Trabeculectomy + Phaco, 0 (0%) At 36 mo: Trabectome + Phaco, 25 (53%); Trabeculectomy + Phaco, 8 (29%)	N = 76 eyes (76 patients) **Inclusion criteria:** Age ≥ 20 y; POAG, exfoliation glaucoma, or other secondary OAG (including normal-tension glaucoma); operation performed by a single designated surgeon; >12 mo follow-up **Exclusion criteria:** History of ocular surgery except cataract surgery; concurrent surgery (including goniosynechialysis or vitrectomy) except cataract surgery Note: Data included in this report are from a subgroup of the complete sample.	Trabectome + Phaco Trabeculotomy + Phaco	**Clinical effectiveness:** IOP (Goldmann applanation tonometer; mean value of 2 measurements at baseline, NR at follow-up), number of glaucoma medications **Safety:** None	3
Marco et al. 2017[82] Canada Funding source: None	Retrospective cohort T-tests and Wilcoxon rank sum; Chi-squared test, or Fisher's exact test *Follow-up:* 6 mo	N = 53 eyes (53 patients) **Inclusion criteria:** Consecutive patients undergoing ECP + Phaco and age-matched patients undergoing Trabeculectomy + Phaco	ECP + Phaco Trabeculectomy + Phaco (with MMC)	**Clinical effectiveness:** IOP, number of glaucoma medications, VA (Snellen VA converted to logMAR) **Safety:** IOP spike (≥ 6 mm Hg from baseline), intraoperative	3, 4

Study Citation, Country, Funding Source	Study Design, Analytical Approach, Duration	Patient Characteristics — Sample Size, Inclusion and Exclusion Criteria	Intervention(s) and Comparator(s)	Outcomes	Relevant for Clinical Research Question(s)
	Loss to follow-up, n: 14 (not included in the sample of N = 53)	**Exclusion criteria:** NR		complications, complications in early (< 30 d) and late (≥ 30 d) post-operative periods	

2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; ALT = argon laser trabeculoplasty; ANOVA = analysis of variance; ARMD = age-related macular degeneration; BCDVA = best corrected-distance visual acuity; BCVA = best-corrected visual acuity; BGI = Baerveldt glaucoma implant; CACG = chronic angle-closure glaucoma; C:D = cup-to-disc ratio; CDVA = corrected-distance visual acuity; CVA = cerebral vascular accident; d = day; dB = decibel; DIOP = diurnal intraocular pressure; ECP = endoscopic cyclophotocoagulation; GDD = glaucoma drainage device; GDD-2 = second Baerveldt glaucoma implant 250 or 350; GI = glaucoma index; HFV = Humphrey visual field; Hydrus = Hydrus Microstent; IOL = intraocular lens; IOP = intraocular pressure; IQR = inter-quartile range; ITT = intention-to-treat; KDB = Kahook Dual Blade; mo = month; LASEK = laser subepithelial keratomileusis; LASIK = laser in situ keratomileusis; LP = light perception; MANOVA = multivariate analysis of variance; MDALL = Medical Devices Active Licence Listing; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; NA = not applicable; NEI VFQ-25 = National Eye Institute-Visual Functioning Questionnaire - 25; NLP = no light perception; NR = not reported; OAG = open-angle glaucoma; PACG = primary angle-closure glaucoma; Phaco = phacoemulsification; Phaco-ECP = phacoemulsification plus endoscopic cyclophotocoagulation; POAG = primary open-angle glaucoma; PRK = photorefractive keratectomy; PXF = pseudoexfoliative glaucoma; QoL = quality of life; RCT = randomized controlled trial; RK = radial keratectomy; SD = standard deviation; SITA = Swedish Interactive Threshold Algorithm; SLT = selective laser trabeculoplasty; Trab + Phaco = Trabeculectomy with mitomycin C + Phacoemulsification; VA = visual acuity; VF = visual field; wk = week; y = year.

Appendix 9: Validity of Intraocular Pressure Outcome Measure

Aim

To summarize the validity of the following outcome measures:

- goldmann applanation tonometry (GAT)
- intraocular pressure (IOP).

Findings

Goldmann Applanation Tonometry

GAT is considered the gold standard in measuring IOP and its use is recommended by the Canadian Ophthalmological Society glaucoma guidelines and the UK National Institute for Health and Care Excellence glaucoma guidelines.[3,207-209]

The reliability of IOP measurement using GAT has been established.[207,208] In a study conducted by Dielemans et al.,[208] 62 patients (mean age 69.6 years), with and without glaucoma, were enrolled to measure inter- and intra-observer variation in IOP measurements in both eyes. Two observers measured the IOP three consecutive times, with 10 minutes between each measurement. The investigators calculated the median IOP, standard deviation (SD), and coefficient of variation for each set of three measurements. The mean difference in the median IOP measurements, and the correlation between the median IOP readings between the two investigators, were used to report on the inter-observer variation. The mean difference between the first IOP reading and the subsequent readings was used as a measure of intra-observer reliability. Also, the mean difference between the first IOP reading and the other two was compared between the two observers as a measure of inter-observer reliability. The results showed a 1.60 mm Hg (SD: 2.15) mean difference in median IOP measurements between observers. The reported correlation coefficient between observers was 0.87 for the left eye and 0.75 for the right eye. The mean difference in median IOP within observers was 1.50 mm Hg (SD: 1.96). The mean difference between first IOP readings from each set of three was 1.79 mm Hg (SD: 2.41) between observers and 1.64 (SD: 2.07) within observers. The authors reported that using the median of three IOP readings reduced the variability of the reading by about 10%. The authors concluded that a median of three measurements may be more reliable than a single reading, as this approach reduced the variability of the reading by about 10%. However, the clinical importance of this decrease in variability is unclear.[208]

A second study conducted by Sudesh et al. examined accuracy and variability in IOP measurement using GAT.[207] In this study, 16 patients were enrolled and eight tonometrists (observers) were randomly assigned to receive GAT training or no training. An observer conducted four consecutive IOP readings on one eye, followed by four consecutive readings by another observer on the same eye. Subsequently, the second observer conducted four IOP readings on the other eye, followed by four readings from the first observer. The mean IOP reading in trained versus untrained tonometrists and the mean IOP readings from each individual tonometrist were reported. The authors reported that the difference in mean IOP reading in trained versus untrained tonometrists was 1.12 mm Hg (standard error [SE]: 0.44). The first set of four readings had a higher mean IOP than the second set of readings (difference 0.71 mm Hg, SE: 0.19 mm Hg). The authors also compared the mean IOP from

four readings between observers. They reported that the difference in mean IOP was 2 mm Hg or more for 26% of observers and 3 mm Hg or more for 19% of observers.[207]

These two studies suggest that GAT produces reliable IOP readings. Variability in IOP measurements is around 1 mm Hg to 2 mm Hg, as indicated by the available evidence, and depends on the observer and timing of measurement.

Intraocular Pressure

Validity and reliability of IOP measurement depends on the tool used to make the IOP readings. No minimal clinically important difference was identified in the published literature. Instead, the Canadian Ophthalmological Society recommends assigning an IOP upper threshold as a goal of therapy based on the severity of glaucoma, as follows:[3]

Suspect in whom a clinical decision is made to treat: 24 mm Hg with at least 20% reduction from baseline:

- early: 20 mm Hg with at least 25% reduction from baseline
- moderate: 17 mm Hg with at least 30% reduction from baseline
- advanced: 14 mm Hg with at least 30% reduction from baseline.

The suggested upper limit of target IOP should be modified based on patient's age, life expectancy, quality of life, and risk factors for progression.[3]

Correlation of Intraocular Pressure Lowering With Clinical Outcomes

A 2013 systematic review by the US Preventive Services Task Force assessed the result of medical treatment on visual field loss and optic nerve damage in OAG.[210] The authors reported three systematic reviews and 21 randomized controlled trials (RCTs) that fit the inclusion criteria of the review. The authors indicated that there was high-quality evidence that lowering IOP reduces risk of optic nerve damage and visual field loss. However, insufficient evidence was present on the effect of glaucoma treatment on patient-reported outcomes (quality of life, activity limitation, patient-reported visual loss).

The effect of treating ocular hypertension and open-angle glaucoma compared with no treatment was evaluated in a 2005 systematic review and meta-analysis.[211] The study included a meta-analysis of five RCTs of patients with ocular hypertension, and the results indicated that reducing IOP decreased the rate of progression to glaucoma compared with no treatment (hazard ratio: 0.56; 95% confidence interval, 0.39 to 0.81). In addition, the meta-analysis of two of the included RCTs indicated that treatment of glaucoma reduced the rate of progression of visual field loss compared with no treatment (hazard ratio: 0.65; 95% confidence interval, 0.49 to 0.87). No formal quality assessment was performed in this systematic review.

Clinical Correlation of Lack of Adherence and Intraocular Pressure Changes

Lack of treatment adherence may result in an increase in measured IOP. For instance, a 2010 prospective observational study surveyed the characteristics of 113 patients with OAG or ocular hypertension using a specific electronic device measuring the number of drops instilled each day after eight weeks of use. The authors of the study reported that, at the end of the eight-week period, patients with low compliance had a mean IOP of 17.7 mm Hg (SD: 5.3), while patients with mid to high compliance had a mean IOP of 15.7 mm Hg (SD: 3.3) (i.e., an approximately 2 mm Hg greater IOP in patients with low compliance).[146] The

authors of the study cautioned against generalizing the results of the survey to the general glaucoma population, as the sample was not recruited randomly, patients knew their compliance was being evaluated, and the duration of assessment was short.[146]

In another study, the mean IOP was found to be 22.9 mm Hg in noncompliant patients versus 18.5 mm Hg in compliant patients.[212] In this study, compliance and glaucoma awareness were assessed in 100 Greek patients taking eye drops for glaucoma; it was determined that 56% of patients had satisfactory treatment compliance, with a mean IOP of 18.6 mm Hg (SD: 3.5), in contrast to a mean IOP of 22.9 mm Hg (SD: 3.7) in noncompliant patients.[212]

Therefore, there is a high level of uncertainty and insufficient evidence to assume that lack of compliance translates into a particular difference in IOP.

Conclusion

Using GAT to measure IOP is considered the gold standard by several professional bodies, including the Canadian Ophthalmological Society. Evidence suggests that GAT provides reliable measurements. However, there is a potential variation of 1 mm Hg to 2 mm Hg with measurement, which may depend on operator and time of measurement. A systematic review and meta-analysis of five RCTs of patients with ocular hypertension and open-angle glaucoma found that reducing IOP decreased the rate of progression to glaucoma compared with no treatment.

Appendix 10: Baseline Patient Characteristics — Clinical Review

Table 29: Baseline Patient Characteristics[a] — Clinical Review

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
Research Questions 1 and 2						
MIGS Vs. Pharmacotherapy						
Vold et al. 2016[58]	Sample size: N = 101 eyes (101 patients) 2x iStent, n = 54 Travoprost, n = 47 Age: 2x iStent: 64.5 y ± 11.1 y Travoprost: 62.0 y ± 11.3 y *P* = NR Sex: n = 44 female; n = 57 male Race: Caucasian	Type of eyes: Phakic Type of glaucoma: POAG, n = 100; PXF, n = 1 Note: the patient with PXF was excluded from the analysis. Glaucoma severity: NR	Previous ocular procedures: None Comorbidities: NR	2x iStent: 25.5 ± 2.5 Travoprost: 25.1 ± 4.6 *P* = NR	None	VF mean deviation (dB): 2x iStent: –7.5 ± 8.8 Travoprost: –5.8 ± 7.7 *P* = NR BCVA (Snellen), n (%): 2x iStent: 20/40 or better, 40 (74%); 20/100 or better, 52 (96%); 20/200 or better, 54 (100%) Travoprost: 20/40 or better, 39 (83%); 20/100 or better, 47 (100%); 20/200 or better, 47 (100%) *P* = NR
Fea et al. 2014[36]	Sample size: N = 192 eyes (192 patients) 2x iStent Inject, n = 94	Type of eyes, n (%): 2x iStent Inject: Phakic, 92 (98%) Pseudophakic, 2 (2%) Latanoprost + Timolol:	Previous ocular procedures: NR Comorbidities: Cataract; others NR	2x iStent Inject: 25.2 ± 1.4 Latanoprost + Timolol: 24.8 ± 1.7	NR	NR

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Two medications, n = 98 Age: 2x iStent Inject: 64.5 y ± 10.3 y (range: 26 y to 83 y) Latanoprost + Timolol: 64.3 y ± 9.8 y (range: 39 y to 83 y) *P* = NR Sex: n = 107 female; n = 85 male Race, n (%): 2x iStent Inject: White, 94 (100%) Latanoprost + Timolol: White, 98 (100%)	Phakic, 95 (97%) Pseudophakic, 3 (3%) Type of glaucoma: Per-protocol, OAG Glaucoma severity: NR		*P* = NR		
MIGS Vs. Laser Therapy						
Fea et al. 2017[62]	Sample size: N = 56 eyes (56 patients) Hydrus, n = 31 eyes (31 patients) SLT, n = 25 eyes (25 patients)	Type of Eyes, n (%): Hydrus: Phakic, 20 (65%); Pseudophakic, 11 (35%) SLT: Phakic, 17 (68%); Pseudophakic, 8 (32%)	Previous ocular procedures: Hydrus: SLT, n = 1 SLT: None *P* = 0.36 Comorbidities: NR	Hydrus: 23.09 ± 5.08 SLT: 23.18 ± 2.15 *P* = 0.93	Hydrus: 2.29 ± 0.83 SLT: 2.48 ± 0.92 *P* = 0.42	VF mean deviation (dB): Hydrus: –8.43 ± 6.84 SLT: –3.04 ± 0.65 *P* < 0.001 VA (logMAR):

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Age: Hydrus: 70.8 y ± 11.83 y SLT: 69.0 y ± 11.28 y *P* = 0.56 Sex: n = 29 female; n = 27 male *P* = 0.10 Race: NR	*P* = 0.79 Type of glaucoma: Per-protocol, POAG Glaucoma severity: NR				Hydrus: 0.25 ± 0.15 SLT: 0.30 ± 0.1 *P* = 0.14
MIGS Vs. Another MIGS						
Katz et al. 2018[59] and Katz et al. 2015[60]	Sample size: N = 119 eyes (119 patients) iStent, n = 38 2x iStent, n = 41 3x iStent, n = 40 Age: iStent: 68.1 y ± 9.1 y (range: 49 y to 83 y) 2x iStent: 67.8 y ± 9.3 y (range: 51 y to 83 y)	Type of Eyes, n: iStent: Phakic, 37; Pseudophakic, 1 2x iStent: Phakic, 41; Pseudophakic, 0 3x iStent: Phakic, 38; Pseudophakic, 1 *P* = NR Type of Glaucoma, n: iStent: POAG, 38; PXF, 0 2x iStent: POAG, 40; PXF, 1	Previous ocular procedures: NR Comorbidities: NR	Medicated IOP: iStent: 19.8 ± 1.3 2x iStent: 20.1 ± 1.6 3x iStent: 20.4 ± 1.8 *P* = NR Unmedicated (post-washout) IOP: iStent: 25.0 ± 1.1 2x iStent: 25.0 ± 1.7	iStent: 1.71 ± 0.61 2x iStent: 1.76 ± 0.54 3x iStent: 1.51 ± 0.69 *P* = NR	VF mean deviation (dB): iStent: –4.72 ± 4.42 2x iStent: –5.20 ± 5.65 3x iStent: –4.81 ± 4.22 *P* = NR BCVA (logMAR): iStent: 0.28 ± 0.34 2x iStent: 0.39 ± 0.40 3x iStent:

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	3x iStent: 60.9 y ± 8.1 y (range: 49 y to 85 y) *P* = NR Sex: n = 53 female; n = 65 male Race: Caucasian	3x iStent: POAG, 39; PXF, 0 *P* = NR Glaucoma severity: Per-protocol, mild to moderate		3x iStent: 25.1 ± 1.9 *P* = NR		0.24 ± 0.35 *P* = NR
MIGS Vs. Filtration Surgery						
ECP Vs. Glaucoma Drainage Device						
Murakami et al. 2017[63]	Sample size: N = 73 eyes (73 patients) ECP, n = 25 GDD-2, n = 48 (BGI 250, n = 26; BGI 350, n = 22) Age: ECP: 59.2 y ± 17.3 y (range: 13 y to 87 y) GDD-2: 60.6 y ± 15.6 y (range: 27 y to 88 y) *P* = 0.73 Sex: n = 31 female; n = 42 male	Type of eyes: Pseudophakic Type of Glaucoma: ECP: POAG, n = 12; CACG, n = 3; juvenile onset, n = 1; secondary, n = 9; steroid, n = 0; congenital, n = 0 GDD-2: POAG, n = 18; CACG, n = 12; juvenile onset, n = 2; secondary, n = 13; steroid, n = 1; congenital, n = 2 Between-group differences, all *P* > 0.05	Previous ocular procedures: BGI 350 (all patients); others NR Comorbidities: NR	ECP: 24.0 ± 6.2 GDD-2: 23.5 ± 8.1 *P* = 0.85	Median, range: ECP: 3, 0 to 4 GDD-2: 4, 0 to 5 *P* = 0.22	VF mean deviation: ECP (n = 10): –13.94 ± 6.32 GDD-2 (n = 23): –17.33 ± 8.68 *P* = 0.29 VF, PSD: ECP (n = 10): 6.96 ± 3.05 GDD-2 (n = 23): 6.71 ± 3.07 *P* = 0.86 VA, median (range): ECP: 20/300 (20/20-LP)

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Race: NR	Glaucoma severity: NR				*GDD-2:* 20/300 (20/25-LP) *P* = 0.35
Lima et al. 2004[61]	Sample size: N = 68 eyes (68 patients) ECP, n = 34 AGI, n = 34 Age: ECP: 53.76 y ± 10.4 y AGI: 56.64 y ± 11.33 y *P* = 0.4 Sex: n = 29 female; n = 39 male Race, n: ECP: White, 24; black, 10; Asian, 0 AGI: White, 22; black, 10; Asian, 2 *P* = NR	Type of eyes: Pseudophakic Type of Glaucoma, n (%): ECP: Neovascular, 14 (41.17%); Pseudophakic, 10 (29.41%); associated with penetrating Keratoplasty, 8 (23.52%); associated with Vitreo-Retinal surgery, 2 (5.88%) AGI: Neovascular, 13 (38.23%); Pseudophakic, 10 (29.41%); associated with Penetrating Keratoplasty, 10 (29.41%); associated with Vitreo-Retinal surgery, 1 (2.9%) *P* = 0.4 Glaucoma severity: NR	Previous ocular procedures: Type of procedures not reported; number of procedures as follows: ECP: 3.1 ± 2.2 AGI: 3.2 ± 2.0 *P* = 0.6 Comorbidities: NR	ECP: 41.61 ± 3.42 AGI: 41.32 ± 3.03 *P* = 0.5	ECP: 3.0 ± 1.3 AGI: 3.5 ± 1.0 *P* = 0.7	VA (LogMAR): ECP: 0.67 ± 0.24 AGI: 0.69 ± 0.25 *P* = 0.8

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
Trabectome (or 2x iStent Inject) Vs. Trabeculectomy						
Pahlitzsch et al. 2017[25]	Sample size: N = 88 eyes (88 patients) Trabectome, n = 43 2x iStent Inject, n = 20 Trabeculectomy, n = 25 Age: Trabectome: 72.8 y ± 8.8 y 2x iStent Inject: 68.6 y ± 16.4 y Trabeculectomy: 74.2 y ± 9.1 y *P* = 0.107 Sex: n = 53 female; n = 35 male Race: Caucasian	Type of eyes: NR Type of glaucoma: OAG (specific type[s] not reported) Glaucoma severity: NR	Previous ocular procedures: NR Comorbidities: Trabectome (n = 10): controlled hypertension, n = 9; mild dysfibrinogenemia defect without clinical impairment or bleeding complications, n = 1 2x iStent Inject (n = 1): controlled hypertension, n = 1 Trabeculectomy (n = 3): atopic dermatitis, n = 2; controlled hypertension, n = 1	Trabectome, 19.1 2x iStent Inject, 21.3 MIGS (Trabectome and 2x iStent Inject groups combined), 20.5 Trabeculectomy, 28.0 Trabeculectomy vs. MIGS, *P* = 0.097	Trabectome: 2.62 2x iStent Inject: 2.45 MIGS: 2.5 Trabeculectomy: 2.32 Trabeculectomy vs. MIGS: *P* = 0.476	VA (logMAR): Trabectome : 0.3 2x iStent Inject : 0.3 MIGS: 0.3 Trabeculectomy: 0.32 Trabeculectomy vs. MIGS: *P* = 0.609
Jea et al. 2012[64]	Sample size: N = 217 eyes (217 patients) Trabectome, n = 115 Trabeculectomy, n = 102	Type of eyes, n (%): Trabectome: Phakic, 75 (65.2%); Pseudophakic, 40 (34.8%) Trabeculectomy: Phakic, 67 (65.7%);	Previous ocular procedures, n (%): Trabectome: ALT, 8 (7.0%); SLT, 29 (25.2%), ALT and SLT, 18 (15.7%)	Trabectome: 28.1 ± 8.6 (range: 14 to 52) Trabeculectomy: 26.3 ± 10.9 (range: 10 to 52)	Trabectome: 3.3 ± 1.3 Trabeculectomy: 3.4 ± 1.0 *P* = 0.289	VA (logMAR): Trabectome: 0.34 ± 0.40 Trabeculectomy: 0.63 ± 0.82 *P* = 0.001

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Age: Trabectome: 63.6 y ± 16.6 y Trabeculectomy: 67.3 y ± 17.1 y *P* = 0.156 Sex: n = 113 female; n = 104 male Race, n (%): Trabectome: White, 86 (74.8%); African American, 14 (12.2%); Hispanic, 9 (7.8%); Asian, 6 (5.2%) Trabeculectomy: White, 71 (69.6%); African American, 17 (16.7%); Hispanic, 8 (7.8%); Asian, 6 (5.9%) *P* = 0.822	Pseudophakic, 35 (34.3%) *P* = 0.942 Type of glaucoma: Trabectome: POAG, 78 (67.8%); PXF, 16 (13.9%); pigment dispersion syndrome, 9 (7.8%); pigmentary, 7 (6.1%); uveitic, 5 (4.3%) Trabeculectomy: POAG, 71 (69.6%); PXF, 12 (11.8%); pigment dispersion syndrome, 6 (5.9%); pigmentary, 8 (7.8%); uveitic, 5 (4.9%) *P* = 0.940 Glaucoma severity: NR	Trabeculectomy: ALT, 4 (3.9%); SLT, 21 (20.6%), ALT and SLT, 6 (5.9%) *P* = 0.031 Comorbidities, n (%): Trabectome: Hypertension, 41 (35.7%); Diabetes, 16 (13.9%) Trabeculectomy: Hypertension, 43 (42.2%); diabetes, 18 (17.6%) *P* = 0.333 (hypertension) *P* = 0.461 (diabetes)	*P* = 0.190		
Xen45 Vs. Trabeculectomy						
Schlenker et al. 2017[65]	Sample size: N = 354 eyes (293 patients) Xen45, n = 185 eyes (159 patients) Trabeculectomy, n = 169	Type of eyes: NR Type of glaucoma: Xen45, n (%): POAG, 106 (57.3%); PXF, 38 (20.5%); pigment dispersion, 10 (5.4%);	Previous ocular procedures, n (%): Xen45: Laser peripheral iridotomy, 13 (7.0%); cataract surgery, 63 (34.1%); laser trabeculoplasty, 97	Median IOP [IQR]: Xen45: 24.0 [19.0, 30.0] Trabeculectomy: 24.0 [19.0, 32.0] *P* = 0.32	NR	VF mean deviation, median (IQR): Xen45, –6.9 (–13.6 to –3.3) Trabeculectomy: –6.0 (–16.0 to –2.8)

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	eyes (139 patients) Age: Xen45 (median age, IQR): 65.0 y, 53.7 y to 73.6 y Trabeculectomy (median age, IQR): 67.2 y, 59.2 y to 74.8 y *P* = 0.038 Sex: n = 178 female; n = 176 male Race, n (%): XEN 45: White, 148 (80.0%); Asian, 18 (9.7%); black, 8 (4.3%); Latino and otherwise unspecified, 11 (6.0%) Trabeculectomy: White, 131 (77.5%); Asian, 20 (11.8%); black, 13 (7.7%); Latino and otherwise unspecified, 5 (3.0%) *P* = 0.42	PACG, 0 (0%); combined mechanisms, 13 (7.1%); normal tension, 4 (2.2%); juvenile OAG, 10 (5.4%); other, 4 (2.2%) Trabeculectomy, n (%): POAG, 96 (56.8%); PXF, 42 (24.8%); pigment dispersion, 10 (5.9%); PACG, 4 (2.4%); combined mechanisms, 7 (4.1%); normal tension, 4 (2.4%); juvenile OAG, 2 (1.2%); other, 4 (2.4%) *P* = 0.15 Glaucoma severity: Xen45, n (%): mild, 85 (45.9%); moderate, 44 (23.8%); advanced, 56 (30.3%)	(52.4%) Trabeculectomy: Laser peripheral iridotomy, 20 (11.8%); cataract surgery, 56 (33.1%); laser trabeculoplasty, 50 (29.6%) P values for between-group differences: Laser peripheral iridotomy, *P* = 0.095; cataract surgery, *P* = 0.91; laser trabeculoplasty, *P* < 0.0001 Comorbidities, n (%): Diabetes: Xen45, 18 (9.7%); Trabeculectomy, 15 (8.9%), *P* = 0.86; others NR	> 21 mm Hg, n (%): Xen45, 109 (58.9%) Trabeculectomy, 103 (60.9%) *P* = 0.75		*P* = 0.96 VA (logMAR), median (IQR): Xen45, 0.2 (0.1 to 0.3) Trabeculectomy: 0.2 (0.1 to 0.6) *P* = 0.039 BCVA 0.4 logMAR or worse, n (%): Xen45, 40 (21.6%) Trabeculectomy: 54 (32.0%) *P* = 0.031

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
		Trabeculectomy, n (%): mild, 83 (49.1%); moderate, 25 (14.8%); advanced, 61 (36.1%) *P* = 0.093				
Research Questions 3 and 4						
MIGS + Phaco Vs. Phaco Alone						
ECP + Phaco Vs. Phaco Alone						
Kang et al. 2017[72]	Sample size: N = 124 eyes (114 patients) ECP + Phaco, n = 62 eyes (10 patients had bilateral surgery) Phaco, n = 62 eyes Age: ECP + Phaco, 76 y ± 12 y Phaco, 74 y ± 11 y *P* = NR Sex: n = 61 female; n = 53 male Race: NR	Type of eyes: NR Type of glaucoma: NR; OAG (including normal tension, PXF and pigmentary) were eligible Glaucoma severity: NR	Previous ocular procedures: ECP + Phaco: 15 patients (27.8%) had previous glaucoma procedures (13 Trabeculectomy with or without MMC, 1 Argon laser trabeculoplasty, 1 transscleral cyclodiode laser) Phaco: None Comorbidities: Cataract; others NR	ECP + Phaco: 20.4 ± 6.25 Phaco: NR	ECP + Phaco: 2.7 ± 0.9 Phaco: NR	VF (dB), mean (range): ECP + Phaco: –17.01 (–2.44 to –30.2); Phaco: NR

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
Perez Bartolome et al. 2017[73]	Sample size: N = 99 eyes (99 patients) ECP + Phaco, n = 69 Phaco, n = 30 Age: ECP + Phaco: 73.94 y ± 8.75 y (range: 52 y to 90 y) Phaco: 71.6 y ± 4.65 y (range: 60 y to 80 y) *P* = 0.096 Sex: n = 48 female; n = 51 male Race, n (%): ECP + Phaco: Caucasian, 40 (57.97%); black, 22 (31.88%); Asian or mixed race, 7 (10.15%) Phaco: Caucasian, 11 (36.66%); black, 15 (50%); Asian or mixed race, 4 (13.34%) *P* = 0.144	Type of eyes: NR Type of glaucoma: Per-protocol, POAG Glaucoma severity: NR as categorical variable; HVF mean deviation meant to reflect "disease severity" and was significantly greater in the ECP + Phaco group (see last column) Note: The Phaco group included those with early-stage glaucoma; the ECP + Phaco group included those with uncontrolled glaucoma or previous failed surgery.	Previous ocular procedures, n (%): ECP + Phaco: None, 48 (69.56%); Trabeculectomy, 9 (13.04%); needling, 3 (4.35%); SLT, 4 (5.79%); GDD, 3 (4.35%); transscleral cyclophotocoagulation, 2 (2.91%); total with previous surgery, 21 (30.4%) Phaco: None, 27 (90%); Trabeculectomy, 2 (6.66%); needling, 0 (0%); SLT, 1 (3.33%); GDD, 0 (0%); transscleral cyclophotocoagulation, 0 (0%); total with previous surgery, 3 (10.0%) *P* = 0.028 Comorbidities: Cataract; others NR	Values reported in study Table 1 (and text): ECP + Phaco: 21.48 ± 5.41 (range: 12 to 38) Phaco: 18.43 ± 3.68 (range: 10 to 24) *P* = 0.005 Values reported in study Table 2: ECP + Phaco: 21.48 ± 5.56 Phaco: 18.43 ± 3.68 *P* = NR	Values reported in study Table 1: ECP + Phaco: 2.62 ± 0.82 (range: 1 to 4) Phaco: 1.2 ± 0.8 (range: 0 to 3) *P* < 0.001 Values reported in study Table 2: ECP + Phaco: 2.61 ± 0.82 Phaco: 1.2 ± 0.805 *P* = NR	VF - HFV mean deviation (dB): ECP + Phaco: –13.36 ± 7.05 (range: –0.98 to –30.79) n = 68 Phaco: –4.74 ± 2.68 (range: –1.45 to –13) n = 25 *P* < 0.001 VA (logMAR): Values reported in study Table 1: ECP + Phaco: 0.33 ± 0.25 (range: 0.1 to 1.0) Phaco: 0.44 ± 0.3 (range: 0.1 to 1.0) *P* = 0.079 Values reported in study Table 2: ECP + Phaco: 0.33 ± 0.25

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
						Phaco: 0.42 ± 0.2 *P* = NR
Sheybani et al. 2015[74]	Sample size: N = 141 eyes (141 patients) ECP + Phaco, n = 83 Phaco, n = 58 Age: ECP + Phaco: 75 y (range: 54 y to 91 y) Phaco: 73 y (range: 42 y to 90 y) *P* = 0.186 Sex: n = 62 female; n = 79 male Race, n (%): ECP + Phaco: African American, 27 (33%); white/other, 56 (67%) Phaco: African American, 11	Type of eyes: NR Type of glaucoma: Per-protocol, OAG Glaucoma severity: Per-protocol, mild to moderate	Previous ocular procedures: None Comorbidities: Cataract; others NR	IOP average over 3 visits: ECP + Phaco: 17.6 ± 9.0 Phaco: 16.1 ± 4.2 *P* = 0.083	ECP + Phaco: 2.0 (range: 0 to 3) Phaco: 0.4 (range: 0 to 3) *P* < 0.001	BCVA (logMAR): ECP + Phaco: 0.382 Phaco: 0.358 *P* = 0.608

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	(19%); white/other, 47 (81%) *P* = NS					
Siegel et al. 2015[75]	Sample size: N = 313 eyes (161 patients) ECP + Phaco, n = 261 eyes (134 patients) Phaco, n = 52 eyes (27 patients) Age: ECP + Phaco: 74.8 y ± 8.0 y Phaco: Reported as 78.0 y ± 8.1 y in a table, and as 78.1 y ± 8.1 y in the text *P* = 0.06 Sex: n = 100 female; n = 61 male Race, n (%): ECP + Phaco: Caucasian, 90 (67.2%); African American, 39 (29.1%); other, 5 (3.7%)	Type of eyes: NR Type of glaucoma, n (%): ECP + Phaco: POAG, 113 (84.4%); CACG, 3 (2.2%); normal-tension glaucoma, 13 (9.7%); other OAG, 5 (3.7%) Phaco: POAG, 15 (55.6%); CACG, 2 (7.4%); normal-tension glaucoma, 5 (18.5%); other OAG, 5 (18.5%) *P* = 0.54 Glaucoma severity: Per-protocol, mild to moderate	Previous ocular procedures: NR Comorbidities: Cataract; others NR	ECP + Phaco: 17.2 ± 4.8 Phaco: 17.7 ± 4.4 *P* = 0.52	ECP + Phaco: 1.3 ± 0.6 Phaco: 1.5 ± 0.7 Reported as *P* = 0.22 in study Table 1 and *P* = 0.02 in study Table 2	Median VA (Snellen): ECP + Phaco: 20/50 Phaco: 20/60 *P* = 0.10

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Phaco: Caucasian, 18 (66.7%); African American, 8 (29.6%); other, 1 (3.7%) *P* = 0.10					
Francis et al. 2014[84]	Sample size: N = 160 eyes (160 patients) ECP + Phaco, n = 80 Phaco alone, n = 80 Age: ECP + Phaco: 70.0 y ± 6.3 y (range: 55 y to 84 y) Phaco alone: 69.7 y ± 6.9 y (range: 56 y to 84 y) *P* = 0.76 Sex: n = 75 female n = 85 male Race: NR	Type of eyes: NR Type of glaucoma: POAG Glaucoma severity: Per-protocol, mild to moderate	Previous ocular procedures: NR Comorbidities: Cataract; others NR	ECP + Phaco: 18.1 ± 3.0 Phaco alone: 18.1 ± 3.0 *P* = 1.0	ECP + Phaco: 1.5 ± 0.8 Phaco alone: 2.4 ± 1.0 *P* < 0.001	NR
1x or 2x iStent + Phaco Vs. Phaco Alone						
El Wardani et al. 2015[76]	Sample size: N = 131 eyes (105 patients)	Type of eyes: NR	Previous ocular procedures: NR	iStent + Phaco: 17.5 2x iStent + Phaco: 17.0	iStent + Phaco: 1.8 2x iStent + Phaco: 2.1	Median VA: iStent + Phaco: 0.4

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	iStent + Phaco, n = 31 eyes (27 patients) 2x iStent + Phaco, n = 22 eyes (21 patients) Phaco alone, n = 78 eyes (61 patients) Age: iStent + Phaco: 68.3 y 2x iStent + Phaco: 69.1 y Phaco alone: 71.1 y *P* = NS Sex: n = 64 female eyes; n = 67 male eyes Race: NR	Type of glaucoma, n (%): iStent + Phaco: POAG, 8 (26%); PACG, 13 (42%); PXF, 2 (7%); pigmentary, 1 (3%); ocular hypertension, 6 (19%); normal-tension glaucoma, 1 (3%) 2x iStent + Phaco: POAG, 5 (23%); PACG, 10 (45%); PXF, 2 (9%); pigmentary, 0 (0%); ocular hypertension, 3 (14%); normal-tension glaucoma, 2 (9%) Phaco alone: POAG, 22 (28%); PACG, 37 (47%); PXF, 10 (13%); pigmentary, 2 (3%); ocular hypertension, 6 (8%); normal-tension glaucoma, 1 (1%) *P* = 0.95 Glaucoma severity: Per-protocol, mild to moderate	Comorbidities: NR	Phaco: 16.3 *P* = NS	Phaco: 1.9 *P* = NS	2x iStent + Phaco: 0.5 Phaco: 0.3 *P* = NR

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
Fea et al. 2015[66] and Fea 2010[67]	Sample size: N = 36 eyes (36 patients) iStent + Phaco, n = 12 Phaco, n = 24 Age: iStent + Phaco: 64.5 y ± 3.4 y (range: 60 y to 70 y) Phaco: 64.9 y ± 3.1 y (range: 59 y to 71 y) *P* = NR Sex: n = 23 female; n = 13 male Race: NR	Type of eyes: NR Type of glaucoma: Per-protocol, POAG Glaucoma severity: NR	Previous ocular procedures: Per-protocol, none Comorbidities: NR	IOP before medication washout: iStent + Phaco: 17.9 ± 2.6 Phaco: 17.3 ± 3.0 *P* = 0.512	iStent + Phaco: 2.0 ± 0.9 Phaco: 1.9 ± 0.7 *P* = NS	Per-protocol, VA no better than 0.6 (20/80)
Craven et al. 2012[68] and Samuelson et al. 2011[34]	Sample size: N = 240 eyes (239 patients) iStent + Phaco, n = 117 Phaco alone, n = 123 Age: iStent + Phaco: 74 y ± 8 y	Type of eyes: NR Type of glaucoma: Per-protocol, POAG Additional glaucoma diagnosis: iStent + Phaco: Pigmentary, 4 (3%); PXF, 7 (6%)	Previous ocular procedures: NR Comorbidities, n (%): Per-protocol, cataracts Other ocular comorbidities in complete sample (“*distributed similarly between groups*” p.	Screening IOP (medicated): iStent + Phaco: 18.7 ± 3.3 (range: 9.5 to 24) Phaco alone: 18.0 ± 3.0 (range: 12 to 24) *P* = 0.103	Screening visit Medications: iStent + Phaco: 1.5 ± 0.7 (range: 1 to 3) Phaco alone: 1.5 ± 0.6 (range: 1 to 3) *P* = 0.451	VF PSD (dB): iStent + Phaco: 2.89 ± 1.79 Phaco alone: 2.79 ± 1.90 *P* = NR VF mean deviation (dB): iStent + Phaco: –3.75 ± 3.03

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	(range: 53 y to 88 y) Phaco alone: 73 y ± 9 y (range: 48 y to 88 y) *P* = 0.314 Sex: n = 142 female; n = 98 male Race: iStent + Phaco: American Indian or Alaska Native, 1 (1%); Asian, 1 (1%); black or African American, 15 (13%); Native Hawaiian or Pacific Islander, 1 (1%); Hispanic or Latino, 16 (14%); white, 83 (71%) Phaco alone: American Indian or Alaska Native, 1 (1%); Asian, 0 (0%); black or African American, 19 (15%); Native Hawaiian or Pacific Islander, 0 (0%); Hispanic or Latino, 15 (12%); white, 88 (72%) *P* = 0.891	Phaco alone: Pigmentary, 3 (2%); PXF, 7 (6%) *P* = 0.939 Glaucoma severity: Mild to moderate	462[34]): posterior vitreous detachment, 42 (18%); dry eye, 31 (13%); AMD, 25 (10%)	Unmedicated IOP: iStent + Phaco: 25.2 ± 3.5 (range: 21 to 36) Phaco alone: 25.5 ± 3.7 (range: 22 to 36) *P* = 0.517		Phaco alone: –3.74 ± 3.86 *P* = 0.983 BCVA (logMAR): iStent + Phaco: 0.35 ± 0.21 (range: –0.10 to 1.00) Phaco alone: 0.36 ± 0.26 (range: –0.16 to 1.74) *P* = 0.797

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
Fernandez-Barrientos et al. 2010[69]	Sample size: N = 33 eyes (33 patients) 2x iStent + Phaco, n = 17 Phaco alone, n = 16 Age: 2x iStent + Phaco: 75.2 y ± 7.2 y (range: 63 y to 86 y) Phaco alone: 76.7 y ± 5.8 y (range: 64 y to 89 y) *P* = 0.5 Sex: n = 18 female; n = 15 male Race: NR	Type of eyes: NR Type of glaucoma: Per-protocol, POAG or ocular hypertension Glaucoma severity, n (%): 2x iStent + Phaco: Ocular hypertension, 2 (11.8%); early glaucoma, 7 (41.2%), moderate glaucoma, 4 (23.5%); advanced glaucoma, 3 (17.6%); severe glaucoma, 1 (5.9%) Phaco alone: Ocular hypertension, 1 (6.3%); early glaucoma, 11 (68.8%), moderate glaucoma, 3 (18.8%); advanced glaucoma, 1 (6.3%); severe glaucoma, 0 (0%) *P* = 0.5	Previous ocular procedures: None Comorbidities: Cataract, others NR	Unmedicated IOP: 2x iStent + Phaco: 24.2 ± 1.8 Phaco alone: 23.6 ± 1.5 *P* = 0.18	2x iStent + Phaco: 1.1 ± 0.5 (range: 0 to1) Phaco alone: 1.2 ± 0.7 (range: 0 to2) *P* = 0.66	NR
Hydrus Microstent + Phaco Vs. Phaco Alone						
Samuelson et al. 2018[88]	Sample size: N = 556 eyes (665 patients)	Type of eyes: NR Type of glaucoma: Per-protocol, POAG	Previous ocular procedures, n (%): Hydrus + Phaco: SLT, 58 (15.7%)	Medicated IOP: Hydrus + Phaco: 17.9 ± 3.1 Median: 18.0	Hydrus + Phaco: 1.7 ± 0.9 Phaco alone:	VF mean deviation (dB): Hydrus + Phaco: –3.61 ± 2.49

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Hydrus + Phaco, n = 369 Phaco alone, n = 187 Age: Hydrus + Phaco: 71.1 ± 7.9 y Phaco alone: 71.2 y ± 7.6 y *P* = NS Sex: n = 311 female; n = 245 male Race, n (%): Hydrus + Phaco: Asian, 21 (5.7%); black or African American, 45 (12.2%); white, 291 (78.9%); other, 12 (3.3%) Phaco alone: Asian, 11 (5.9%); black or African American, 15 (8.0%); white, 153 (81.8%); other, 8 (4.3%) *P* = NS	Glaucoma severity: Per-protocol, mild to moderate	Phaco alone: SLT, 28 (15.0%) *P* = NS Comorbidities: Cataract, others NR	Phaco alone: 18.1 ± 3.1 Median: 18.0 *P* = NS Washed-out modified DIOP: Hydrus + Phaco: 25.5 ± 3.0 Phaco alone: 25.4 ± 2.9 *P* = NS	1.7 ± 0.9 *P* = NS	Phaco alone: –3.61 ± 2.60 *P* = NS VF PSD (dB): Hydrus + Phaco: 3.18 ± 2.18 Phaco alone: 3.13 ± 1.85 *P* = NS BCVA (Snellen): Hydrus + Phaco: 20/40 Min, 20/240 Max, 20/14 Phaco alone: 20/40 Min, 20/138 Max, 20/16 *P* = NS

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
Pfeiffer et al. 2015[71]	Sample size: N = 100 eyes (100 patients) Hydrus + Phaco, n = 50 Phaco, n = 50 Age: Hydrus + Phaco: 72.8 y ± 6.6 y Phaco: 71.5 y ± 6.9 y *P* = 0.3498 Sex: n = 51 female; n = 49 male Race, n (%): Hydrus + Phaco: White, 48 (96.0%); Hispanic, 1 (2.0%); Asian, 1 (2.0%) Phaco: White, 49 (98.0%); Hispanic, 0 (0.0%); Asian, 0 (0.0%) All *P* = 1.000	Type of eyes: NR Type of glaucoma, n (%): Hydrus + Phaco: POAG, 45 (90.0%); PXF, 5 (10.0%); Pigmentary glaucoma, 0 (0%); previous trabeculoplasty, 0 (0%) Phaco: POAG, 41 (82.0%); PXF, 8 (16.0%); Pigmentary glaucoma, 1 (2.0%); previous trabeculoplasty, 1 (2.0%) All *P* > 0.39 Glaucoma severity: NR	Previous ocular procedures: One patient had previous trabeculoplasty in the Phaco group; otherwise, NR Comorbidities: NR	Medicated IOP: Hydrus + Phaco: 18.9 ± 3.3 Phaco: 18.6 ± 3.8 *P* = 0.6517 Washed-out DIOP: Hydrus + Phaco: 26.3 ± 4.4 Phaco: 26.6 ± 4.2 *P* = 0.7147	Hydrus + Phaco: 2.0 ± 1.0 Phaco: 2.0 ± 1.1 *P* = 0.7619	VF mean deviation: Hydrus + Phaco: –5.6 ± 5.4 Phaco: –8.4 ± 7.8 *P* = 0.0449 VF PSD: Hydrus + Phaco: 5.1 ± 4.6 Phaco: 5.2 ± 4.3 *P* = 0.9589 BCVA: Hydrus + Phaco: 20/44 (range: 20/13 to 20/160) Phaco: 20/40 (range: 20/16 to 20/400) *P* = 0.3784

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
Other Comparisons (From Single Studies)						
Vold et al. 2016[70] Note: The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from this study;[37,38] however, at the time of report publication, this device was still active in the MDALL and is therefore included in this report.	Sample size: N = 505 eyes (505 patients) CyPass Micro-Stent + Phaco, n = 374 Phaco alone, n = 131 Age: CyPass Micro-Stent + Phaco, 70 y ± 8 y Phaco alone, 70 y ± 8 y *P* > 0.05 Sex: n = 269 female; n = 236 male Race, n (%): CyPass Micro-Stent + Phaco: American Indian or Alaska Native, 4 (1%); Asian, 5 (1%); black or African American, 36 (10%); Hispanic or Latino, 15 (4%); Native Hawaiian or other Pacific Islander, 0 (0%); white,	Type of eyes: NR Glaucoma type: Per-protocol, POAG Glaucoma severity: "*mild-to-moderate*" (p. 2103); explicit values NR	Previous ocular procedures: Per-protocol, none except laser trabeculoplasty (numbers NR) Comorbidities: Cataract; no other ocular pathologies; others NR	Unmedicated baseline DIOP: CyPass Micro-Stent + Phaco: 24.4 ± 2.8 (range: 21.0 to 33.0) Phaco alone: 24.5 ± 3.0 (range: 21.0 to 32.3) *P* > 0.05	CyPass Micro-Stent + Phaco: 1.4 ± 0.9 Phaco alone: 1.3 ± 1.0 *P* > 0.05	VF mean deviation (dB): CyPass Micro-Stent + Phaco: –3.37 ± 2.90 (range: –15.5 to 2.03) *Phaco alone:* –3.77 ± 3.07 (range: –15.5 to 0.79) *P* > 0.05 Medium BAT or BCVA (where BAT unavailable) at screening: CyPass Micro-Stent + Phaco: Mean logMAR: 0.517 ± 0.263 Mean Snellen: 20/66 Phaco alone: Mean logMAR: 0.541 ± 0.268 Mean Snellen: 20/70 *P* > 0.05

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	314 (84%); other (Caribbean), 0 (0%) Phaco alone: American Indian or Alaska Native, 2 (2%); Asian, 1 (1%); black or African American, 11 (8%); Hispanic or Latino, 7 (5%); Native Hawaiian or other Pacific Islander, 1 (1%); white, 108 (82%); other (Caribbean), 1 (0%) *P* > 0.05					
MIGS + Phaco Vs. A Different MIGS + Phaco						
Goniotomy With Kahook Dual Blade + Phaco Vs. iStent + Phaco						
Dorairaj et al. 2018[86]	Sample size: N = 435 eyes (318 patients) KDB + Phaco, n = 237 iStent + Phaco, n = 198 Age: KDB + Phaco: 70.1 y ± 8.9 y iStent + Phaco: 71.3 y ± 8.1 y *P* = 0.169	Type of eyes: NR Type of glaucoma, n (%): KDB + Phaco: POAG, 178 (75.1%); exfoliation, 17 (7.2%); Pigmentary, 15 (6.3%); angle closure, 14 (5.9%); normal tension, 6 (2.5%); C=congenital, 1 (0.9%); others, 6 (2.5%)	Previous ocular procedures: NR Comorbidities: Cataract; others NR	KDB + Phaco: 17.9 ± 4.4 iStent + Phaco: 16.7 ± 4.4 *P* = NR	KDB + Phaco: 1.7 ± 0.9 iStent + Phaco: 1.9 ± 0.9 *P* > 0.05	BCVA (logMAR): Complete sample: 0.4 ± 0.3

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Sex: n = 257 female; n = 178 male Race, n (%): KDB + Phaco: Caucasian, 110 (46.4%); Hispanic, 63 (26.6%); black, 42 (17.7%); Asian, 14 (5.9%); others, 8 (3.4%) iStent + Phaco: Caucasian, 119 (60.1%); Hispanic, 34 (17.2%); black, 34 (17.2%); Asian, 7 (3.5%); others, 4 (2.0%) *P* = 0.038	iStent + Phaco: POAG, 177 (89.4%); exfoliation, 3 (1.5%); Pigmentary, 4 (2.0%); angle closure, 0 (0.0%); normal tension, 4 (2.0%); congenital, 0 (0.0%); others, 10 (5.1%) *P* < 0.001 Glaucoma severity, n (%; defined by ICD-9 definitions): KDB + Phaco: mild, 117 (49.4%); moderate, 120 (50.6%) iStent + Phaco: Mild, 85 (49.1%); moderate, 88 (50.9%) *P* = 0.095				
Trabectome + Phaco Vs. 2x iStent + Phaco						
Kurji et al. 2017[79]	Sample size: N = 70 eyes (55 patients) Trabectome + Phaco, n = 36 eyes (30 patients) 2x iStent + Phaco,	Type of eyes: NR Type of glaucoma, number of patients: Trabectome + Phaco, POAG, n = 14; PXF, n = 16 patients	Previous ocular procedures, number of eyes: Trabectome + Phaco: SLT, n = 17 ALT, n = 3	Trabectome + Phaco: 20.92 ± 5.07 2x iStent + Phaco: 17.47 ± 4.87 *P* = 0.026	Trabectome + Phaco: 2.25 ± 1.34 2x iStent + Phaco: 2.15 ± 1.21 *P* = 0.21	VA: Trabectome + Phaco: 0.36 ± 0.27 logMAR iStent + Phaco: NR *P* > 0.05

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	n = 34 eyes (25 patients) Age: Trabectome + Phaco: 72.41 y ± 9.63 y 2x iStent + Phaco: 75.02 y ± 10.34 y *P* = 0.42 Sex: n = 28 female; n = 27 male Race: NR	2x iStent + Phaco: POAG, n = 14; PXF, n = 11 patients Glaucoma Severity, number of eyes: Trabectome + Phaco: Mild, n = 5 moderate, n = 20 advanced, n = 11 2x iStent + Phaco: Mild, n = 5 moderate, n = 14 advanced, n = 14 *P* = 0.67 for each level of severity	2x iStent + Phaco: SLT, n = 14 ALT, n = 0 Between-group differences in previous ocular procedures: SLT, *P* = 0.68; ALT, *P* = 0.07 Comorbidities: Cataract; others NR			
Khan et al. 2015[78]	Sample size: N = 101 eyes (101 patients) Trabectome + Phaco, n = 52 2x iStent + Phaco, n = 49 Age: Trabectome + Phaco: 76.1 y ± 12.1 y 2x iStent + Phaco: 77.5 y ± 11.9 y *P* = 0.55	Type of eyes: NR Type of glaucoma, n (%): Trabectome + Phaco: POAG, 50 (96%); pigmentary dispersion, 1 (2%); PXF, 1 (2%) 2x iStent + Phaco: POAG, 38 (78%); pigmentary dispersion, 0 (0%); PXF, 11 (22%) *P* values for between-group comparisons:	Previous ocular procedures: NR Comorbidities: NR	Trabectome + Phaco: 20.6 ± 6.8 2x iStent + Phaco: 19.6 ± 5.2 (SD reported as 5.2 in a table and as 5.3 in the abstract and text) *P* = 0.37	Trabectome + Phaco: 2.90 ± 1.10 2x iStent + Phaco: 2.86 ± 0.91 *P* = NR Median [IQR]: Trabectome + Phaco: 3.0 [2.0, 4.0] 2x iStent + Phaco: 3.0 [2.0, 3.0] *P* = 0.53	VF mean deviation (dB): Trabectome + Phaco: –8.6 ± 9.7 2x iStent + Phaco: –11.5 ± 8.0 *P* = 0.17

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Sex: n = 58 female; n = 43 male Race, n (%): Trabectome + Phaco: White, 36 (70%); Other, 16 (30%) 2x iStent + Phaco: White, 34 (69%); Other, 15 (31%) *P* = 0.34	POAG, *P* = 0.47; pigmentary dispersion, *P* = 1; PXF, *P* = 0.007 Glaucoma severity: Per-protocol, any severity				
Trabectome + MICS Vs. 2x iStent Inject + MICS						
Gonnermann et al. 2017[77]	Sample size: N = 50 eyes (25 patients) Trabectome + MICS, n = 25 2 iStent Inject + MICS, n = 25 Age: Complete sample: 73.8 y ± 7.8 y Sex: n = 14 female; n = 13 male Race: Caucasian	Type of eyes: NR Type of glaucoma: OAG (POAG, n = 19 patients; PXF, n = 8 patients) Glaucoma severity: Trabectome + MICS: Mild: 13 (52%); moderate: 12 (48%); advanced: 0 (0%); 2 iStent inject + MICS: Mild: 12 (48%); moderate: 13 (52%) advanced: 0 (0%)	Previous ocular procedures: No surgery or laser Comorbidities: Cataract; no other ocular or systemic diseases	Trabectome + MICS: 22.3 ± 3.7 (range: 18 to 27) 2 iStent inject + MICS: 21.3 ± 4.1 (range: 16 to 34) *P* = NR	Trabectome + MICS: 2.1 ± 1.0 (range: 0 to 4) 2 iStent inject + MICS: 2.0 ± 0.9 (range: 0 to 4) *P* = NR	BCVA, number (%): Trabectome + MICS: ≥ 20/40: 12 (48%); 20/50 to 20/100: 13 (52%); ≥ 20/200: 0 (0%) 2 iStent inject + MICS: ≥ 20/40: 14 (56%) 20/50 to 20/100: 11 (44%) ≥ 20/200: 0 (0%) *P* = NR

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
Different Numbers of iStents + Phaco						
Vlasov and Kim 2017[80]	Sample size: N = 69 eyes (69 patients) iStent + Phaco, n = 39 2x iStent + Phaco, n = 30 Age: iStent + Phaco, 74.23 y ± 10.2 y 2x iStent + Phaco, 70.26 y ± 9.64 y *P* = 0.0974 Sex: n = 27 female; n = 42 male Race: NR	Type of eyes: NR Type of glaucoma: Per-protocol, POAG, PXF, pigmentary dispersion glaucoma (numbers NR) Glaucoma severity: Per-protocol, any stage	Previous ocular procedures: NR Comorbidities: NR	Values reported in study Table 1: iStent + Phaco, 16.67 ± 4.1 2x iStent + Phaco, 18.33 ± 3.99 *P* = 0.0870 Values reported in study Table 2: iStent + Phaco, 16.67 ± 3.82 2x iStent + Phaco, 18.33 ± 3.99 *P* = 0.4996	iStent + Phaco: 2.33 ± 1.4 2x iStent + Phaco : 2.37 ± 1.30 *P* = 0.9205	BCVA (logMAR): iStent + Phaco: 0.32 ± 0.23 2x iStent + Phaco: 0.38 ± 0.25 *P* = 0.7484
Belovay et al. 2012 [83]	Sample size: N = 53 eyes (47 patients) 2x iStent + Phaco, n = 28 eyes (26 patients) 3x iStent + Phaco, n = 25 eyes (23 patients)	Type of eyes: NR Type of glaucoma, n (%): 2x iStent + Phaco: POAG, 21 (75%); PXF, 7 (25%); mixed mechanism, 0 (0%) 3x iStent + Phaco: POAG, 16 (64%);	Previous ocular procedures, n (%): 2x iStent + Phaco: LPI, 4 (14%); ALT, 6 (21%); SLT, 7 (25%) 3x iStent + Phaco: LPI, 7 (28%); ALT, 3 (12%); SLT, 10 (40%)	2x iStent + Phaco: 17.3 ± 4.0 3x iStent + Phaco: 18.6 ± 4.0 *P* = 0.24	2x iStent + Phaco: 2.8 ± 0.8 3x iStent + Phaco: 2.6 ± 1.2 *P* = 0.70	CDVA, n (%): 2x iStent + Phaco: 20/40 or better, 6 (21%); 20/50 to 20/100, 15 (54%); 20/200 or worse, 7 (25%) 3x iStent + Phaco: 20/40 or better, 8 (32%); 20/50 to 20/100, 11 (44%); 20/200 or worse, 6 (23%)

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Age: 2x iStent + Phaco: 78.8 y ± 7.0 y 3x iStent + Phaco: 75.0 y ± 7.3 y *P* = 0.07 Sex: n = 33 female n = 14 male Race, n (%): 2x iStent + Phaco: White, 18 (69%); black, 4 (15%); South Asian, 2 (8%); Far East Asian, 2 (8%) 3x iStent + Phaco: White, 11 (48%); black, 4 (17%); South Asian, 5 (22%); Far East Asian, 3 (13%) *P* = 0.43	PXF, 7 (28%); mixed mechanism, 2 (8%) *P* values for between-group comparisons: POAG, *P* = 0.55; PXF, *P* = 1.00; mixed mechanism, *P* = NR Glaucoma severity, n: Overall sample: Mild, 8; moderate, 23; advanced, 22	*P* values for between-group comparisons: LPI, *P* = 0.31; ALT, *P* = 0.47; SLT, *P* = 0.38 Comorbidities: Cataract 2x iStent + Phaco: AMD, 4 (14%); high myopia, 1 (4%); suprasellar lesion, 1 (4%); branch vein occlusion, 1 (4%); diabetic retinopathy, 0 (0%); AMD scar, 0 (0%); optic nerve head drusen, 1 (4%) 3x iStent + Phaco: AMD, 0 (0%); High myopia, 1 (5%); suprasellar lesion, 1 (5%); branch vein occlusion, 0 (0%); diabetic retinopathy, 1 (4%); AMD scar, 1 (4%); optic nerve head drusen, 0 (0%) *P* = NR			*P* = 0.76 VF mean deviation (dB): 2x iStent + Phaco: –12.6 ± 7.1 3x iStent + Phaco: –10.2 ± 8.1 *P* = 0.24 VF, mean PSD (dB): 2x iStent + Phaco: 7.9 ± 3.4 3x iStent + Phaco: 5.9 ± 4.1 *P* = 0.06

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
ECP + iStent + Phaco Vs. iStent + Phaco						
Ferguson et al. 2017[81]	Sample size: N = 101 eyes (76 patients) ECP + iStent + Phaco, n = 51 eyes (34 patients) iStent + Phaco, n = 50 eyes (42 patients) Age: ECP + iStent + Phaco: 69.65 y ± 11.46 y iStent + Phaco: 74.30 y ± 9.41 y *P* = 0.03 Sex: n = 54 female; n = 47 male Race: NR	Type of eyes: NR Type of glaucoma: OAG Glaucoma severity: ECP + iStent + Phaco: Mild, n = 9; moderate, n = 16; severe, n = 26 Stent + Phaco: Mild, n = 23; moderate, n = 22; severe, n = 5	Previous ocular procedures: NR Comorbidities: Cataract; others NR	ECP + iStent + Phaco: 21.49 ± 9.59 iStent + Phaco: 20.66 ± 3.23 *P* = 0.56	ECP + iStent + Phaco: 1.78 ± 0.99 iStent + Phaco: 1.68 ± 0.84 *P* = NR	NR
ECP + Phaco Vs. Trabectome + Phaco						
Moghimi et al. 2018[89]	Sample size: N = 61 eyes (61 patients) ECP + Phaco, n = 35 Trabectome + Phaco, n = 26	Type of eyes: NR Type of glaucoma, n (%): ECP + Phaco: POAG, 20 (57.1%); PXF, 15 (42.9%) Trabectome + Phaco: POAG, 16 (61.5%);	Previous ocular procedures: Per-protocol, no surgical history Comorbidities: Cataract; others NR	ECP + Phaco: 20.6 ± 5.4 (range: 12 to 30) Trabectome + Phaco: 18.7 ± 4.7 (range: 11 to 30) *P* = 0.30	ECP + Phaco: 2.0 ± 1.0 (range: 0 to 4) Trabectome + Phaco: 1.3 ± 1.2 (range: 0 to 4) *P* = 0.06	VF (dB): ECP + Phaco: –9.1 ± 5.7 Trabectome + Phaco: –8.0 ± 4.3 *P* = NS

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Age: ECP + Phaco: 69.58 y ± 9.85 y (range: 48 y to 84 y) Trabectome + Phaco: 61.84 y ± 15.03 y (range: 30 y to 85 y) *P* = 0.01 Sex: n = 24 female; n = 37 male Race: Iranian	PXF, 10 (38.5%) Glaucoma severity, n (%): ECP + Phaco: Mild, 13 (37.1%); moderate, 9 (25.7%); severe, 13 (37.1%) Trabectome + Phaco: Mild, 9 (34.6%); moderate, 9 (34.6%); severe, 8 (30.8%) *P* = NR				
MIGS + Phaco Vs. Filtration Surgery + Phaco						
Ting et al. 2018[87]	Sample size: N = 19 eyes (19 patients) Trabectome + Phaco, n = 10 eyes (10 patients) Trabeculectomy + Phaco, n = 9 eyes (9 patients) Age: Trabectome + Phaco: 71.3 y ± 6.3 y Trabeculectomy + Phaco: 67.4 y ± 5.9 y	Type of eyes: NR Type of glaucoma, n (%): Trabectome + Phaco: POAG, 7 (70%); PXF, 3 (30%) Trabeculectomy + Phaco: POAG, 6 (67%); PXF, 3 (33%) *P* = 0.88 Glaucoma severity, n (%): Trabectome + Phaco:	Previous ocular procedures: Trabectome + Phaco: SLT, 2 (20%); ALT, 1 (10%) Trabeculectomy + Phaco: SLT, 1 (11%); ALT, 0 (0%) *P* = 0.31 Comorbidities: Cataract; others NR	Trabectome + Phaco: 20.0 ± 5.3 Trabeculectomy + Phaco: 23.1 ± 6.4 *P* = 0.22	Trabectome + Phaco: 1.80 ± 1.31 Trabeculectomy + Phaco: 1.40 ± 1.13 *P* = 0.59	NR

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	P = 0.23 Sex: n = 9 female; n = 10 male Race, n (%): Trabectome + Phaco: Caucasian, 9 (90%); African American, 1 (10%); Hispanic, 0 (0%) Trabeculectomy + Phaco: Caucasian, 8 (89%); African American, 0 (0%); Hispanic, 1 (11%) *P* = 0.37	Mild, 3 (30%); moderate, 6 (60%); advanced, 1 (10%) Trabeculectomy + Phaco: Mild, 4 (44%); moderate, 3 (33%); advanced, 2 (22%) *P* = 0.49				
Kinoshita-Nakano et al. 2018[85]	Sample size: N = 76 eyes (76 patients) Trabectome + Phaco, n = 47 eyes (47 patients) Trabeculotomy + Phaco, n = 29 eyes (29 patients) Age: Trabectome + Phaco: 71.0 y ± 8.6 y (range: 52 y to 85 y)	Type of eyes: NR Type of glaucoma, n: Trabectome: POAG, 27; exfoliation, 15; secondary, 5 Trabeculotomy: POAG, 16; exfoliation, 10; secondary, 3 *P* = 0.97 Glaucoma severity: NR	Previous ocular procedures: NR Comorbidities: NR	Trabectome + Phaco: 21.0 ± 5.7 (range: 13 to 37.5) Trabeculotomy + Phaco: 23.0 ± 7.0 (range: 15 to 40) *P* = 0.33	Trabectome + Phaco: 3.2 ± 0.9 (range: 1 to 5) Trabeculotomy + Phaco: 3.1 ± 0.8 (range: 2 to 5) *P* = 0.49	VF mean deviation (dB): Trabectome + Phaco: –11.60 ± 8.12 Trabeculotomy + Phaco: –15.38 ± 8.39 *P* = 0.071 VA (logMAR): Trabectome + Phaco: 0.16 ± 0.29 Trabeculotomy + Phaco: 0.31 ± 0.49

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
	Trabeculotomy + Phaco: 72.5 y ± 6.2 y (range: 55 y to 81 y) *P* = 0.42 Sex: n = 42 female; n = 34 male Race: Japanese					*P* = 0.29
Marco et al. 2017[82]	Sample size: N = 53 eyes (53 patients) ECP + Phaco, n = 24 Trab + Phaco (Trabeculectomy with MMC + Phaco), n = 29 Age: ECP + Phaco: 68.8 y ± 11.3 y (range: 43 y to 84 y) Trab + Phaco: 73.1 y ± 13.2 y (range: 38 y to 92 y) *P* = 0.144 Sex: n = 27 female; n = 26 male Race: NR	Type of eyes: NR Type of glaucoma, n (%): ECP + Phaco: POAG, 12 (50.0%); PXF, 2 (8.3%); Neovascular, 1 (4.2%); Uveitic, 1 (4.2%); PACG, 6 (25.0%); Plateau iris, 2 (8.3%) Trab + Phaco: POAG, 21 (72.4%); PXF, 4 (13.8%); Neovascular, 0 (0%); Uveitic, 1 (3.5%); PACG, 3 (10.3%); Plateau iris, 0 (0%) *P* values for between-group comparisons all P > 0.05	Previous ocular procedures, n (%): ECP + Phaco: ALT/SLT, 3 (12.5%); LPI, 6 (25.0%); Trabeculectomy, 2 (8.3%); Tube, 1 (4.2%) Trab + Phaco: ALT/SLT, 3 (10.3%); LPI, 5 (17.2%); Trabeculectomy, 1 (3.5%); Tube, 0 (0%) *P* values for between-group comparisons all *P* > 0.05 Comorbidities: Past ocular history: ECP + Phaco: PDR, 2 (8.3%); AMD, 2 (8.3%);	ECP + Phaco: 19.9 ± 10.2 Trab + Phaco: 19.2 ± 7.2 *P* = 0.589	ECP + Phaco: 2.5 ± 1.2 Trab + Phaco: 2.7 ± 1.2 *P* = 0.667	VA (logMAR): ECP + Phaco: 0.656 ± 0.59 Trab + Phaco: 0.620 ± 0.58 *P* = 0.670

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
		Glaucoma severity: NR Note: Those with healthy conjunctiva were assigned to the Trab + Phaco group; those with thinner conjunctiva underwent ECP + Phaco.	RVO, 1 (4.2%); Uveitis, 1 (4.2%); RD, 1 (4.2%) Trab + Phaco: PDR, 0 (0%); AMD, 1 (3.5%); RVO, 2 (6.9%); Uveitis, 2 (6.9%); RD, 0 (0%) *P* values for between-group comparisons all *P* > 0.05 Other comorbidities, n (%): ECP + Phaco: Asthma, 3 (12.5%); diabetes mellitus, 3 (12.5%); hypertension, 5 (20.8%); CVA, 1 (4.2%); thyroid, 0 (0%) Trab + Phaco: asthma, 0 (0%); diabetes mellitus, 2 (6.9%); hypertension, 8 (27.6%); CVA, 0 (0%); thyroid, 1 (3.5%)			

Study Citation	Sample Size, Age, Sex, Race	Type of Eyes,[b] Type of Glaucoma, Glaucoma Severity	Previous Ocular Procedure(s), Relevant Comorbidities	Baseline IOP (mm Hg), Mean ± SD	Baseline Number of Glaucoma Medications, Mean ± SD	Baseline Visual Field, Visual Impairment, and/or Visual Acuity
			P values for between-group comparisons all *P* > 0.05			

1x = one device; 2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; ALT = argon laser trabeculoplasty; AMD = age-related macular degeneration; BAT = brightness acuity test; BCVA = best-corrected visual acuity; BGI = Baerveldt glaucoma implant; CACG = chronic angle-closure glaucoma; CDVA = corrected-distance visual acuity; CVA = cerebral vascular accident; dB = decibel; DIOP = diurnal intraocular pressure; ECP = endoscopic cyclophotocoagulation; GDD = glaucoma drainage device; GDD-2 = second Baerveldt glaucoma implant 250 or 350; GI = glaucoma index; HFV = Humphrey visual field; Hydrus = Hydrus Microstent; ICD-9 = International Classification of Diseases 9; IOL = intraocular lens; IOP = intraocular pressure; IQR = inter-quartile range; KDB = Kahook Dual Blade; logMAR = logarithm of the minimum angle of resolution; LP = light perception; LPI = laser peripheral iridotomy; MDALL = Medical Devices Active Licence Listing; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; NR = not reported; NS = non-significant; OAG = open-angle glaucoma; PACG = primary angle-closure glaucoma; PDR = proliferative diabetic retinopathy; Phaco = phacoemulsification; Phaco-ECP = phacoemulsification plus endoscopic cyclophotocoagulation; POAG = primary open-angle glaucoma; PSD = pattern standard deviation; PXF = pseudoexfoliative glaucoma; RD = retinal detachment; RVO = retinal vein occlusion; SD = standard deviation; SLT = selective laser trabeculoplasty; Trab + Phaco = Trabeculectomy with mitomycin C + Phacoemulsification; VA = visual acuity; VF = visual field; vs. = versus; y = year.

[a] Unless otherwise stated, all values are means ± standard deviations.

[b] Whether eyes contained the natural (phakic) lens or were pseudophakic, if reported.

Appendix 11: Primary Study Author Disclosures — Clinical Review

Table 30: Primary Study Author Disclosures

Author Disclosures	Citations — Research Questions 1 and 2	Citations — Research Questions 3 and 4
Financial support from industry (non-study related or study support)	Vold et al. 2016[58] Fea et al. 2014[36] Katz et al. 2018 [59] Katz et al. 2015[60] Schlenker et al. 2017[65]	Samuelson et al. 2011[34] Craven et al. 2012[68] Vold et al. 2016[70] Pfeiffer et al. 2015[71] Khan et al. 2015[78] Dorairaj et al. 2018[86] Fernandez-Barrientos et al. 2010[69] Samuelson et al. 2018[88]
Non-financial support from industry	Vold et al. 2016[58] Katz et al. 2015[60]	NA
Receipt of non-speaker honoraria	NA	Khan et al. 2015[78]
Consultant for, employee, or board member of industry	Fea et al. 2017[62] Katz et al. 2018[59] Katz et al. 2015[60] Jea et al.[64] Schlenker et al. 2017[65]	Francis et al. 2014[84] Samuelson et al. 2011[34] Craven et al. 2012[68] Vold et al. 2016[70] Pfeiffer et al. 2015[71] Ferguson et al. 2017[81] Khan et al. 2015[78] Belovay et al. 2012[83] Dorairaj et al. 2018[86] Samuelson et al. 2018[88]
Shareholder, stock holder, patent holder, or equity owner in manufacturer company	Katz et al. 2018[59]	Samuelson et al. 2011[34] Craven et al. 2012[68] Vold et al. 2016[70] Pfeiffer et al. 2015[71] Dorairaj et al. 2018[86]
Study devices provided by industry	Vold et al. 2016[58] Fea et al. 2014[36] Katz et al. 2018[59]	Samuelson et al. 2011[34] Craven et al. 2012[68] Fea 2010[67] Fea et al. 2015[66]
Receipt of lecture fees/honoraria or give lectures for manufacturer	Katz et al. 2018[59]	Vold et al. 2016[70] Pfeiffer et al. 2015[71] Khan et al. 2015[78] Ferguson et al. 2017[81] Kinoshita et al. 2018[85]
Industry assisted in publication fees, preparation of the manuscript, data analysis, or editorial assistance	Vold et al. 2016[58] Fea et al. 2014[36] Katz et al. 2018[59]	Vold et al. 2016[70] Fea 2010[67]
No conflict of interest	Murakami et al. 2017[63] Pahlitzsch et al. 2017[25]	Kang et al. 2017[72] Perez et al. 2017 [73] Sheybani et al. 2015[74] Siegel et al. 2015[75] Fea 2010[67] Fea et al. 2015[66] Ting et al. 2018[87] Marco et al. 2017[82] Gonnermann et al. 2017[77]

Author Disclosures	Citations — Research Questions 1 and 2	Citations — Research Questions 3 and 4
		Kurji et al. 2017[79] El Wardani et al. 2015[76] Moghimi et al. 2017[89]
No declaration	Lima et al. 2004[61]	Vlasov and Kim 2017[80]
Some declarations made using acronyms that were not defined	NA	Fernandez-Barrientos et al. 2010[69] Samuelson et al. 2011[34]

NA = Not applicable.

Appendix 12: Detailed Outcome Data — Clinical Review

Table 31: Detailed Outcome Data — Clinical Review

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
Research Questions 1 and 2			
MIGS Vs. Pharmacotherapy			
Vold et al. 2016[58]	**Clinical effectiveness** **IOP** (mm Hg), mean, 2x iStent and Travoprost respectively: • baseline: 25.5; 25.1 • 1 mo: 15.2; 15.0 • 3 mo: 15.0; 14.4 • 6 mo: 14.2; 13.8 • 12 mo: 13.7; 13.9 • 18 mo: 13.5; 14.6 • 24 mo: 13.8; 15.0 • 30 mo: 13.7; 15.4 • 36 mo: 14.6; 15.3 **IOP** (mm Hg) in **eyes without additional medical therapy** (subset), mean (n), 2x iStent and Travoprost respectively: • baseline: 25.5 (54); 25.1 (47) • 1 mo: 15.2 (54); 15.0 (47) • 3 mo: 15.0 (52); 14.1 (44) • 6 mo: 14.2 (50); 13.7 (42) • 12 mo: 13.7 (50); 13.9 (42) • 18 mo: 13.5 (49); 14.5 (42) • 24 mo: 13.8 (47); 15.1 (41) • 30 mo: 13.7 (45); 15.5 (39) • 36 mo: 14.5 (32); 15.7 (28) **Proportion of eyes** (%) **with IOP ≤ 18 mm Hg without additional medical therapy,** 2x iStent and Travoprost respectively: • 12 mo: 94; 89 • 24 mo: 90; 87 • 36 mo: 91; 79	• IOP tended to be reduced, and BCVA and VF tended to be improved, at follow-up in both groups, but there were no statistical comparisons • Safety was favourable in both groups	*"In both groups, patients showed substantial IOP reduction and favorable safety through 3 years. these findings support the viability of multiple iStent implantations as an initial treatment option comparable to topical prostaglandin in newly diagnosed POAG,"* p. 169.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	Proportion of eyes (%) **with IOP ≤ 15 mm Hg without additional medical therapy,** 2x iStent and Travoprost respectively: • 12 mo: 75; 72 • 24 mo: 81; 46 • 36 mo: 62; 21 **Proportion of eyes** (%) **with BCVA 20/200 or better,** 2x iStent and Travoprost respectively: • baseline: 100; 100 • 36 mo: 100; 100 **Proportion of eyes** (%) **with BCVA 20/100 or better,** 2x iStent and Travoprost respectively: • baseline: 96; 100 • 36 mo: 90; 88 **Proportion of eyes** (%) **with BCVA 20/40 or better,** 2x iStent and Travoprost respectively: • baseline: 74; 83 • 36 mo: 77; 74 **VF mean deviation (dB)**, mean ± SD, 2x iStent and Travoprost respectively: • baseline: –7.5 ± 8.8; –5.8 ± 7.7 • 12 mo: –7.7 ± 8.9; –6.3 ± 7.6 • 24 mo: –6.0 ± 9.7; –5.5 ± 7.7 • 36 mo: –6.8 ± 7.4; –6.2 ± 6.0 **VF PSD (dB)**, mean ± SD, 2x iStent and Travoprost respectively: • baseline: 4.6 ± 3.3; 3.5 ± 2.6 • 12 mo: 4.4 ± 3.1; 3.5 ± 2.6 • 24 mo: 4.7 ± 3.2; 3.4 ± 2.4 • 36 mo: 4.3 ± 3.1; 3.4 ± 2.4 **Safety** **Complications** in 2x iStent group: • hyphema, n = 1 • iridodialysis with no post-operative ocular sequelae, n = 1 • progression of cataract, n = 11 (20%)		

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	Complications in Travoprost group: • progression of cataract, n = 8 (17%) Note: There were no statistical comparisons in this study.		
Fea et al. 2014[36]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, 2x iStent inject and Latanoprost + Timolol respectively (*P* values NR): • screening (on medications): 21.1 ± 1.7; 20.7 ± 1.7 • baseline (unmedicated): 25.2 ± 1.4; 24.8 ± 1.7 • 1 mo: 13.3 ± 4.1; 12.8 ± 2.6 • 3 mo: 12.8 ± 3.2; 12.5 ± 2.8 • 6 mo: 12.7 ± 3.2; 12.2 ± 2.2 • 9 mo: 12.9 ± 2.9; 12.8 ± 2.9 • 12 mo: 13.0 ± 2.3; 13.2 ± 2.0 **Reduction in IOP from screening** (mm Hg), mean ± SD, 2x iStent inject and Latanoprost + Timolol respectively (*P* values NR): • 1 mo: –7.7 ± 4.2; –7.9, 2.9 • 3 mo: –8.3 ± 3.3; –8.1 ± 2.6 • 6 mo: –8.5 ± 2.8; –8.3 ± 2.4 • 9 mo: –8.2 ± 3.0; –7.7, ± 2.8 • 12 mo: –8.1 ± 2.6; –7.3 ± 2.2 **Reduction in IOP from baseline** (mm Hg), mean ± SD, 2x iStent inject and Latanoprost + Timolol respectively (*P* values NR): • 1 mo: –11.8 ± 4.2; –12.0 ± 2.9 • 3 mo: –12.4 ± 3.4; –12.3 ± 2.8 • 6 mo: –12.5 ± 3.2; –12.6 ± 2.4 • 9 mo: –12.3 ± 3.0; –11.9 ± 2.8 • 12 mo: –12.2 ± 2.5; –11.6 ± 2.2 **Proportion of patients with IOP reduction ≥ 20% at 12 mo vs. unmedicated baseline**, n (%), 2x iStent inject and Latanoprost + Timolol respectively: • 89 (94.7%; 95% CI, 88.0 to 98.3); 88 (91.8%; 95% CI, 84.5 to 96.4), *P* > 0.05	• The reduction of IOP was similar between groups across all time points • Adverse events were not different between groups	*"These data show that the use of iStent inject is at least as effective as two medications, with the clinical benefit of reducing medication burden and assuring continuous treatment with full compliance to implant therapy as well as having a highly favorable safety profile,"* p. 875. *"This study confirms that the iStent inject is a safe and effective implant procedure with a high benefit-to-risk profile and may be a preferable alternative to chronic use of multiple medications in subjects with OAG,"* p. 881.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	Proportion of patients (%) with IOP reduction ≥ 30% at 12 mo vs. unmedicated baseline, 2x iStent inject and Latanoprost + Timolol respectively: • 93.6% (95% CI, 86.6 to 97.6); 88.8 (95% CI, 80.8 to 94.3), *P* > 0.05 **Proportion of patients (%) with IOP reduction ≥ 40% at 12 mo vs. unmedicated baseline,** 2x iStent inject and Latanoprost + Timolol respectively: • 80.9% (95% CI, 71.4 to 88.2); 75.5 (95% CI, 65.8 to 83.6), *P* > 0.05 **Proportion of patients (%) with IOP reduction ≥ 50% at 12 mo vs. unmedicated baseline,** 2x iStent inject and Latanoprost + Timolol respectively: • 53.2% (95% CI, 42.6 to 63.6); 35.7 (95% CI, 26.3 to 46.0), *P* = 0.02 **IOP ≤ 18 mm Hg,** n (%), 2x iStent inject and Latanoprost + Timolol respectively: • 12 mo: 87 (92.6%; 95% CI, 85.3 to 97.0); 88 (89.8%; 95% CI, 82.0 to 95.0), *P* = NR **IOP ≤ 15 mm Hg,** n (%), 2x iStent inject and Latanoprost + Timolol respectively: • 12 mo: 87 (85.1%; 95% CI, 76.3 to 91.6); 88 (81.6%; 95% CI, 72.5 to 88.7), *P* = NR **BCVA** of 20/40 or better (%), 2x iStent inject and Latanoprost + Timolol respectively: • baseline: 84%; 87%, *P* = NR • 12 mo: 79%; 84%, *P* = NR **Safety** **Adverse events** at any point post-operatively, n (%), 2x iStent inject and Latanoprost + Timolol respectively (*P* values NR): • eye burning: 0 (0%), 1 (1%) • IOP decompensation: 1 (1%), 0 (0%) • medication allergy: 0 (0%), 1 (1%) • one stent not visible: 1(1%), 0 (0%) • soreness/discomfort: 1 (1%), 0 (0%)		
MIGS Vs. Laser Therapy			
Fea et al. 2017[62]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD: • Baseline: Hydrus, 23.09 ± 5.08; SLT, 23.18 ± 2.15, between-group *P* = 0.93	• IOP was not different between groups at baseline or follow-up • The reduction in medication use from	*"Both SLT and Hydrus implantation reduced IOP without serious adverse events. Hydrus implantation led to a significant and further*

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	Reduction in IOP from baseline (mm Hg), mean ± SD, Hydrus and SLT respectively (all significantly different from baseline at $P < 0.001$; P values for between-group comparisons): • 1 mo: –4.3 ± 6.79; –6.0 ± 3.29, $P = 0.26$ • 3 mo: –5.5 ± 6.54; –7.1 ± 2.27, $P = 0.27$ • 6 mo: –6.7 ± 5.61; –7.3 ± 3.10, $P = 0.59$ • 12 mo: –6.6 ± 5.62; –7.3 ± 2.53, $P = 0.57$ **Reduction in IOP from baseline** (%), mean ± SD, Hydrus and SLT respectively (all significantly different from baseline at $P < 0.001$; P values for between-group comparisons): • 1 mo: –16 ± 24; –26 ± 14, $P = 0.26$ • 3 mo: –21 ± 25; –30 ± 9, $P = 0.27$ • 6 mo: –27 ± 21; –31 ± 12, $P = 0.59$ • 12 mo: –26 ± 18; –31 ± 10, $P = 0.57$ ○ At 12 mo, number (%) of patients with IOP reduction > 20% from baseline: Hydrus, 27 (90%); SLT, 22 (88%) **Medications** (number), mean ± SD, Hydrus and SLT respectively (P values for between-group comparisons): • baseline: 2.29 ± 0.83; 2.48 ± 0.92, $P = 0.42$ • 12 mo: 0.9 ± 1.04; 2.0 ± 0.91, P = NR **Reduction in medications from baseline** (number), mean ± SD, Hydrus and SLT respectively: • 12 mo: –1.4 ± 0.97 ($P < 0.05$ compared with baseline); –0.5 ± 1.05 ($P > 0.05$ compared with baseline); difference 0.9 medications/patient; between-group $P = 0.001$ **Proportion of patients with zero medications** at 12 mo (%): • Hydrus 47%; SLT, 4%, $P = 0.004$ **VA** (logMAR), mean ± SD, Hydrus and SLT respectively (P values for comparison with baseline where applicable): • baseline: 0.25 ± 0.15; 0.30 ± 0.1, P value for between-group comparison $P = 0.14$ • 12 mo: 0.22 ± 0.1, $P = 0.36$; 0.33 ± 0.12, $P = 0.34$, P value for between-group comparison NR	baseline was greater in the Hydrus vs. SLT group • There was no change in VA from baseline to follow-up in either group • There were few complications overall, and all complications were transient	*reduction in medication dependence at 12 months,"* p. 120. *"…the Hydrus device [was] implanted in more severe glaucomatous patients. Nevertheless, the pertinent findings of the present investigation are the following: (i) Hydrus Microstent provided equivalent IOP reduction to SLT at one year of over 7 mm Hg; and (ii) patients treated with the Hydrus Microstent used significantly less medication at 12 months to maintain target IOP,"* p. 126.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	Safety **Complications**, number (%): Hydrus: • IOP spike, 2 (6.45%) • temporary decrease in VA > 2 lines lasting < 7 d, 3 (9.68%; reasons: corneal edema secondary to IOP spike or hyphema) SLT: • none • eye discomfort (40%)		
MIGS Vs. Another MIGS			
Katz et al. 2018[59] and Katz et al. 2015[60]	**Clinical effectiveness** **IOP** (mm Hg) **while on medications unless otherwise specified**, mean ± SD, for iStent, 2x iStent, and 3x iStent groups respectively (*P* values NR): • screening: 19.8 ± 1.3; 20.1 ± 1.6; 20.4 ± 1.8 • baseline (unmedicated): 25.0 ± 1.1; 25.0 ± 1.7; 25.1 ± 1.9 • 1 mo: 12.2 ± 3.1; 12.5 ± 2.7; 12.0 ± 2.7 • 3 mo: 12.8 ± 2.3; 13.0 ± 2.1; 12.8 ± 2.0 • 6 mo: 13.1 ± 1.7; 13.5 ± 2.3; 12.9 ± 2.0 • 12 mo: 14.4 ± 1.2; 12.8 ± 1.4; 12.2 ± 1.5 • 12-13 mo (after 1 mo medication washout): 14.9 ± 1.9; 13.6 ± 2.1; 12.7 ± 2.1 • 18 mo: 15.6 ± 1.5; 13.8 ± 1.3; 12.1 ± 1.2 • 36-37 mo (after 1 mo medication washout): 17.4 ± 0.9; 15.8 ± 1.1; 14.2 ± 1.5 • 42 mo: 15.0 ± 2.8; 15.7 ± 1.0; 14.8 ± 1.3 **IOP** (mm Hg) **for eyes without medication at 18 mo**, mean ± SD, for iStent (n = 32), 2x iStent (n = 37), and 3x iStent (n = 35) groups respectively (*P* values NR): • 15.93 ± 0.90; 14.07 ± 1.00; 12.24 ± 1.12 **Mean difference in unmedicated IOP between groups** (mm Hg) **at 18 mo:** • 3x iStent vs. iStent: 3.58, 95% CI, 2.66 to 4.49, *P* < 0.001 • 3x iStent vs. 2x iStent: 1.84, 95% CI, 0.96 to 2.73, *P* < 0.001 • 2x iStent vs. iStent: 1.73, 95% CI, 0.83 to 2.64, *P* < 0.001 **Reduction in unmedicated IOP from screening at 18 mo**, mm Hg (%), for iStent, 2x iStent, and 3x iStent groups respectively (*P* values NR):	12 mo follow-up: • The proportion of eyes with an IOP reduction of ≥ 20% from baseline, or with IOP ≤ 18 mm Hg, was similar across groups, but this was not tested statistically • Proportionately more eyes in the *2x* and *3x* iStent groups had an IOP ≤15 mm Hg compared with the iStent group, but this was not tested statistically 18 mo follow-up: • IOP was reduced from baseline in all groups, and the reduction was incrementally greater with increasing numbers of iStents 24 mo follow-up: • BCVA was not different	*"[…] implantation of each additional stent resulted in significantly greater IOP reduction with reduced medication use. Titratability of stents as a sole procedure was shown to be effective and safe, with sustained effect through 18 months postoperatively in OAG not controlled with medication,"* p. 2313.[60] *"The standalone implantation of either single or multiple iStent® device(s) produced safe, clinically meaningful IOP and medication reductions through 42 months postoperatively, with incrementally greater and more sustained reductions in multi-stent eyes,"* p. 255.[59]

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• –3.94 (–19.5%); –5.99 (–29.5%); –8.19 (–39.7%) **Reduction in unmedicated IOP from baseline at 18 mo**, mm Hg (%), for iStent, 2x iStent, and 3x iStent groups respectively (*P* values NR): • –9.04 (–36.1%); –10.77 (–43.2%); –12.61 (–50.6%) **Unmedicated IOP reduction ≥ 20% from baseline at 12 mo post-operative,** n (%) (*P* values NR): • iStent: 33 (89.2%); 95% CI, 74.6 to 97.0% • 2x iStent: 37 (90.2%); 95% CI, 76.9 to 97.3% • 3x iStent: 35 (92.1%); 95% CI, 78.6 to 98.3% **Unmedicated IOP reduction ≥ 20% from baseline at 42 mo post-operative,** n/total (%) (*P* values NR): • iStent: 17/28 (61%) • 2x iStent: 32/35 (91%) • 3x iStent: 32/35 (91%) **Unmedicated IOP ≤ 18 mm Hg at 12 mo post-operative**, n (%) (*P* values NR): • iStent: 33 (89.2%); 95% CI, 74.6 to 97.0% • 2x iStent: 37 (90.2%); 95% CI, 76.9 to 97.3% • 3x iStent: 35 (92.1%); 95% CI, 78,6 to 98.3% **Unmedicated IOP ≤ 15 mm Hg at 12 mo post-operative**, n (%) (*P* values NR): • iStent: 24 (64.9%); 95% CI, 47.5 to 79.8% • 2x iStent: 35 (85.4%); 95% CI, 70.8 to 94.4% • 3x iStent: 35 (92.1%); 95% CI, 78.6 to 98.3% **Number of eyes (%) on medication,** for iStent, 2x iStent, and 3x iStent groups respectively (*P* values NR): • screening: 38 (100%); 41 (100%); 40 (100%) • baseline: 0 (0%); 0 (0%); 0 (0%) • 1 mo: 0 (0%); 0 (0%); 0 (0%) • 3 mo: 1 (2.6%); 0 (0%); 0 (0%) • 6 mo: 3 (7.9%); 1 (2.4%); 1 (2.5%) • 12 mo: 4 (10.8%); 4 (9.8%); 3 (7.9%)	from baseline in any group 42 mo follow-up: • Proportionately more eyes in the 2x and 3x iStent groups had an IOP reduction of ≥ 20% from baseline compared with the iStent group, but this was not tested statistically • The change in VF from screening to 42 mo follow-up was not significantly different from between groups; whether absolute VF was significantly different within groups was not tested statistically Overall: • Medications were stopped immediately after surgery and re-added in a small proportion of patients in each group to control IOP • There were no serious complications	

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 12-13 mo (after 1 mo medication washout): 0 (0%); 0 (0%); 0 (0%) • 18 mo: 4 (11.1%); 4 (9.8%); 3 (7.9%) **VF, mean deviation (dB),** mean ± SD, for iStent, 2x iStent, and 3x iStent groups respectively (*P* values NR): • screening: –4.72 ± 4.42; –5.20 ± 5.65; –4.81 ± 4.22 • 18 mo: –4.9 ± 4.71; –5.96 ± 5.84; –5.24 ± 4.13 • 42 mo: –6.43 ± 4.95; –7.11 ± 5.78; –6.91 ± 5.40 **Change in VF mean deviation (db) at 42 mo vs. screening** for iStent, 2x iStent, and 3x iStent groups respectively (between-group comparison, *P* = 0.40) • –1.42; –1.26; –2.08 **BCVA:** • "*In general, BCVA […] values did not appear to be different at 2 years postoperatively vs preoperative levels"* p. 2317[60] • Values reported as proportion of eyes with BCVA 20/40 or better, 20/100 or better, and 20/200 or better at baseline and months 1, 3, 6, 12, 18, and 42 (with no statistical analyses) **Safety** **Intraoperative adverse events:** None **Perioperative adverse events:** None **Secondary surgical interventions:** • Cataract surgery by 18 mo: iStent, 2; 2x iStent, 0; 3x iStent, 2 • Cataract surgery by 42 mo: iStent, 5; 2x iStent, 2; 3x iStent, 3		
MIGS vs. Filtration Surgery			
ECP Vs. Glaucoma Drainage Device			
Murakami et al. 2017[63]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, ECP and GDD-2 respectively (*P* values for between-group differences): • baseline: 24.0 ± 6.2; 23.5 ± 8.1, *P* = 0.85 • 3 mo: 13.0 ± 3.4; 14.2 ± 5.5, *P* = 0.19 • 6 mo: 14.9 ± 4.9; 15.2 ± 6.3, *P* = 0.98 • 12 mo: 15.4 ± 3.8; 14.2 ± 4.0, *P* = 0.61 • 24 mo: 18.1 ± 7.4; 14.6 ± 3.8, *P* = 0.14 **IOP reduction from baseline** (mm Hg), mean ± SD, ECP and GDD-2 respectively (*P* values for	• IOP and number of medications were significantly reduced from baseline in both ECP and GDD-2 groups at 3 to 24 mo follow-up, but there were no differences between groups at any time point • Complications were not	*"Both ECP and GDD-2 are both effective as second surgeries for refractory glaucoma that has failed a prior aqueous shunt,"* p. 241.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	between-group comparison; all significant vs. baseline at $P < 0.001$ unless otherwise stated): • 3 mo: 11.0 ± 7.7; 9.3 ± 8.9, $P = 0.29$ • 6 mo: 8.7 ± 8.6; 8.3 ± 11.1, $P = 0.64$ • 12 mo: 7.8 ± 6.5; 9.3 ± 8.3, $P = 0.66$ • 24 mo: 7.0 ± 8.8 ($P < 0.05$ for comparison with baseline); 8.9 ± 7.6, $P = 0.52$ **% IOP reduction from baseline** (%), mean ± SD, ECP and GDD-2 respectively (P values for between-group comparison; all significant vs. baseline at $P < 0.001$ unless otherwise stated): • 3 mo: 42.0 ± 20.8; 39.6 ± 20.6, $P = 0.20$ • 6 mo: 32.4 ± 29.3; 35.3 ± 28.6, $P = 0.33$ • 12 mo: 30.8 ± 21.6; 39.6 ± 30.7, $P = 0.56$ • 24 mo: 25.5 ± 34.2 ($P < 0.05$ for comparison with baseline); 38.7 ± 27.8, $P = 0.50$ **Medications** (number), median (range), ECP and GDD-2 respectively (P values for between-group comparisons): • baseline: 3 (0 to 4); 4 (0 to 5), $P = 0.22$ • 3 mo: 2 (0 to 5); 2 (0 to 4), $P = 0.88$ • 6 mo: 1 (0 to 4); 2 (0 to 5), $P = 0.13$ • 12 mo: 1 (0 to 5); 2 (0 to 4), $P = 0.37$ • 24 mo: 2 (0 to 5); 3 (0 to 5), $P = 0.61$ **Medication reduction from baseline** (number), median (mean ± SD), ECP and GDD-2 respectively (P values for between-group comparisons): • 3 mo: 1 (1.4 ± 1.3); 2 (1.6 ± 1.8), $P = 0.57$ • 6 mo: 1 (1.7 ± 1.4); 2 (1.4 ± 1.6), $P = 0.64$ • 12 mo: 2 (1.6 ± 1.5); 1 (1.5 ± 1.8), $P = 0.74$ • 24 mo: 1 (1.5 ± 1.9); 1 (0.9 ± 1.6), $P = 0.50$ **Safety** • There were complications in both groups (hypotony, corneal oedema, high IOP, inflammation, CME), but no difference between groups, $P > 0.05$	different between groups	
Lima et al. 2004[61]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, ECP and AGI respectively (P values for between-group comparisons): • baseline: 41.61 ± 3.42; 41.32 ± 3.03, $P = 0.5$ • 1 wk: 9.5 ± 5.23; 5.38 ± 4.57, $P = 0.04$	• IOP was significantly higher in the ECP vs. AGI group at 1 wk follow-up, not different between groups at 1 mo,	*"[ECP] may be a safe and efficient modality in treating refractory glaucoma compared with [AGI]," p. 237.*

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 1 mo: 11.38 ± 4.99; 10.82 ± 7.60, *P* = 0.4 • 2 mo: 13.41 ± 7.11; 21.88 ± 6.00, *P* = 0.03 • 3 mo: 13.57 ± 6.22; 20.4 ± 5.70, *P* = 0.01 • 4 mo: 13.28 ± 3.88; 16.53 ± 1.50, *P* = 0.03 • 5 mo: 13.64 ± 2.88; 17.1 ± 5.70, *P* = 0.08 • 6 mo: 14.00 ± 3.62; 17.78 ± 5.50, *P* = 0.06 • 12 mo: 15.45 ± 6.54; 16.59 ± 5.37, *P* = 0.4 • 18 mo: 13.93 ± 5.41; 14.38 ± 1.83, *P* = 0.5 • 24 mo: 14.07 ± 7.21 (compared with baseline, *P* < 0.001); 14.73 ± 6.44 (compared with baseline, *P* < 0.001), *P* = 0.7 IOP > 6 mm Hg and < 21 mm Hg (with or without medication), %, for ECP and AGI respectively: • 12 mo: 82.35%; 76.47%, *P* = 0.1 • 24 mo: 73.52%; 70.58%, *P* = 0.5 **Medications** (number), mean ± SD (range), ECP and AGI respectively (*P* values for between-group comparisons): • baseline: 3.0 ± 1.3; 3.5 ± 1.0, *P* = 0.7 • 24 mo: 2.0 ± 1.2; 2.5 ± 1.3, *P* = 0.3 **VA** (LogMar), mean ± SD (range), ECP and AGI respectively (*P* values for between-group comparisons): • baseline: 0.67 ± 0.24; 0.69 ± 0.25, *P* = 0.8 • 12 mo: 0.74 ± 0.42; 0.98 ± 0.61, *P* = 0.1 **Safety** **Complications during study,** n (%), ECP and AGI respectively (*P* values for between-group comparisons): • choroid detachment: 1 (2.94%); 6 (17.64%); *P* = 0.1 • shallow anterior chamber: 0 (0%); 6 (17.64%); *P* = 0.02 • hyphema: 6 (17.64%); 5 (14.7%); *P* = 1.0 • cystic bleb: 0 (0%); 5 (14.7%); *P* = 0.05 • failure of the corneal graft: 1 (2.94%); 4 (11.76%); *P* = 0.3 • tube block: 0 (0%); 2 (5.88%); *P* = 0.4 • corneal touch: 0 (0%); 2 (5.88%); *P* = 0.4 • retina detachment: 1 (2.94%); 2 (5.88%); *P* = 1.0	significantly lower in ECP vs. AGI at 2, 3, and 4 mo, and not different between groups thereafter up to 24 mo; IOP was significantly reduced from baseline at 24 mo in both groups • The proportion of patients meeting the criteria for success was similar between groups at 12 and 24 mo follow-up • The number of medications was not significantly different between groups at 24 mo follow-up • VA was not different between groups at 12 mo follow-up • Complications were similar between groups, except for shallow anterior chamber, which occurred in significantly more patients in the AGI group	*"There was no difference in the success rate between the [AGI] e and ECP in refractory glaucoma. The eyes that underwent Ahmed tube shunt implantation had more complications than those treated with ECP,"* p. 233.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• inflammatory precipitates in anterior chamber: 4 (11.76%); 0 (0%); *P* = 0.1 • tube exposure: 0 (0%); 2 (5.88%); *P* = 0.4 • hypotony: 1 (2.94%); 0 (0%); *P* = 1.0 • endophthalmitis: N/A; 1 (2.94%); *P* = 1.0 • phthisis bulbi: 1 (2.94%); 0 (0%); *P* = 1.0 ○ Note: Some potential complications were not applicable to both interventions.		
Trabectome (or 2x iStent Inject) Vs. Trabeculectomy			
Pahlitzsch et al. 2017[25]	**Clinical effectiveness** **IOP** (mm Hg), mean; Trabectome, 2x iStent Inject, MIGS (Trabectome and 2x iStent Inject groups combined), and Trabeculectomy respectively (*P* values for comparison with baseline unless otherwise specified): • baseline: 19.1; 21.3; 20.5; 28.0; Trabeculectomy vs. MIGS, *P* = 0.097 • 1 d: 12.0 (*P* < 0.001); 11.7 (*P* < 0.001); 12.1 (*P* = NR); 12.7 (*P* <0 .001); Trabeculectomy vs. MIGS, *P* = 0.802 • 6 wk: 17.5 (*P* = 0.217); 15.3 (*P* = 0.005); 16.7 (*P* = NR); 13.6 (*P* = 0.003); Trabeculectomy vs. MIGS, *P* = 0.046 • 3 mo: 16.5 (*P* = 0.063); 14.1 (*P* = 0.005); 15.7 (*P* = NR); 13.3 (*P* = 0.001); Trabeculectomy vs. MIGS, *P* = 0.046 • 6 mo: 14.7 (*P* = 0.001); 16.0 (*P* = 0.068); 14.8 (*P* = NR); 12.9 (*P* = 0.005); Trabeculectomy vs. MIGS, *P* = 0.400 **Medications** (number), mean; Trabectome, 2x iStent Inject, MIGS (Trabectome and 2x iStent Inject groups combined), and Trabeculectomy respectively (*P* values for comparison with baseline unless otherwise specified): • baseline: 2.62; 2.45; 2.5; 2.32; Trabeculectomy vs. MIGS, *P* = 0.476 • 1 d: 2.53 (*P* = 0.317); 2.00 (*P* = 0.024); 1.88 (*P* = NR); 0.21 (*P* = 0.003); Trabeculectomy vs. MIGS, *P* < 0.001 • 6 wk: 2.44 (*P* = 0.070); 1.90 (*P* = 0.026); 1.79 (*P* = NR); 0.44 (*P* = 0.001); Trabeculectomy vs. MIGS, *P* < 0.001 • 3 mo: 2.36 (*P* = 0.132); 1.50 (*P* = 0.157); 1.64 (*P* = NR); 0.61 (*P* = 0.001); Trabeculectomy vs. MIGS, *P* < 0.001 • 6 mo: 2.34 (*P* = 0.227); 2.50 (*P* = 0.317); 1.81 (*P* = NR); 0.50 (*P* = 0.006); Trabeculectomy vs. MIGS, *P* < 0.001	• IOP was significantly reduced from baseline in the 2x iStent Inject and Trabeculectomy groups (but not Trabectome) at 6 wk and 3 mo, and in Trabectome and Trabeculectomy (but not 2x iStent Inject) groups at 6 mo, but there was no significant difference between groups at 6 mo • IOP was significantly lower in the Trabeculectomy vs. MIGS (combined Trabectome and 2x iStent Inject) groups at 6 wk and 3 mo, but not 6 mo • The number of medications was significantly reduced from baseline in the 2x iStent Inject group at 1 d and 6 wk but not 3 mo or 6 mo follow-up, and in the Trabeculectomy group at all follow-up time points, but was not different from	*"In this study cohort, the QoL can be maintained by all three surgical techniques. Patients, however, need lower numbers of topical medications in [Trabeculectomy], which would impact QoL even though it is not included in the NEI-VFQ-25. The decision of the most appropriate surgical technique should be made by including single QoL categories, IOP and glaucoma medication outcome,"* p. 351.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	VA (logMAR), mean; Trabectome, 2x iStent Inject, MIGS (Trabectome and 2x iStent Inject groups combined), and Trabeculectomy respectively (*P* values for comparison with baseline unless otherwise specified): • baseline: 0.3; 0.3; 0.3; 0.32; Trabeculectomy vs. MIGS, *P* = 0.609 • 1 d: 0.3 (*P* = 0.469); 0.2 (*P* = 0.452); 0.3 (*P* = NR); 0.4 (*P* = 0.028); Trabeculectomy vs. MIGS, *P* = 0.011 • 6 wk: 0.2 (*P* = 0.030); 0.16 (*P* = 0.018); 0.2 (*P* = NR); 0.32 (*P* = 0.721); Trabeculectomy vs. MIGS, *P* = 0.223 • 3 mo: 0.25 (*P* = 0.210); 0.16 (*P* = 0.204); 0.22 (*P* = NR); 0.4 (*P* = 0.553); Trabeculectomy vs. MIGS, *P* = 0.284 • 6 mo: 0.26 (*P* = 0.202); 0.2 (*P* = 0.273); 0.22 (*P* = NR); 0.3 (*P* = 0.905); Trabeculectomy vs. MIGS, *P* = 0.907 **Quality of life parameters:** Note: Data for all QoL parameters are presented in order of Trabectome, 2x iStent Inject, MIGS, and Trabeculectomy groups, respectively. **QoL – General health** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 47.0 ± 13.7; 45.0 ± 19.1; 46.3 ± 15.5; 43.0 ± 21.0 ○ *P* values: Trabeculectomy vs. MIGS, 0.546; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.702; Trabeculectomy vs. Trabectome, 0.442; Trabeculectomy vs. 2x iStent Inject, 0.883 **QoL – General vision** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 69.2 ± 16.7; 63.9 ± 18.1; 67.5 ± 17.2; 61.6 ± 21.5 ○ *P* values: Trabeculectomy vs. MIGS, 0.190; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.197; Trabeculectomy vs. Trabectome, 0.112; Trabeculectomy vs. 2x iStent Inject, 0.707 **QoL – Ocular pain** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 71.0 ± 22.0; 71.8 ± 25.6; 71.2 ± 23.0; 75.0 ± 25.7 ○ *P* values: Trabeculectomy vs. MIGS, 0.365; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.619; Trabeculectomy vs. Trabectome, 0.323; Trabeculectomy vs. 2x iStent Inject, 0.641 **QoL – Near activities** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 75.9 ± 25.6; 72.2 ± 28.4; 74.8 ± 26.3; 66.0 ± 28.5	baseline in the Trabectome group at any follow-up time point • The number of medications was lower in Trabeculectomy vs. MIGS at all follow-up time points • VA was significantly greater in Trabeculectomy vs. MIGS at 1 d post-operative, but was not different between groups at all other time points • None of the 12 QoL parameters were significantly different between Trabeculectomy and MIGS groups at 6 mo • There was only one between-group difference in any QoL parameter at 6 mo; "colour vision" was significantly higher in Trabectome vs. Trabeculectomy	

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	○ *P* values: Trabeculectomy vs. MIGS, 0.140; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.296; Trabeculectomy vs. Trabectome, 0.116; Trabeculectomy vs. 2x iStent Inject, 0.418 **QoL – Distance activities** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 73.4 ± 25.3; 65.2 ± 26.7; 70.8 ± 25.8; 61.6 ± 28.7 ○ *P* values: Trabeculectomy vs. MIGS, 0.143; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.172; Trabeculectomy vs. Trabectome, 0.076; Trabeculectomy vs. 2x iStent Inject, 0.670 **QoL – Social functioning** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 85.7 ± 22.0; 82.2 ± 27.1; 84.6 ± 23.5; 72.5 ± 30.8 ○ *P* values: Trabeculectomy vs. MIGS, 0.060; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.160; Trabeculectomy vs. Trabectome, 0.059; Trabeculectomy vs. 2x iStent Inject, 0.232 **QoL – Mental health** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 73.5 ± 27.0; 70.5 ± 27.0; 72.5 ± 26.8; 64.5 ± 29.7 ○ *P* values: Trabeculectomy vs. MIGS, 0.157; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.297; Trabeculectomy vs. Trabectome, 0.129; Trabeculectomy vs. 2x iStent Inject, 0.441 **QoL – Role difficulties** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 71.5 ± 30.6; 64.3 ± 35.6; 69.2 ± 32.2; 67.0 ± 33.2 ○ *P* values: Trabeculectomy vs. MIGS, 0.749; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.760; Trabeculectomy vs. Trabectome, 0.603; Trabeculectomy vs. 2x iStent Inject, 0.888 **QoL – Dependency** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 85.4 ± 22.5; 82.4 ± 27.5; 84.5 ± 23.9; 75.3 ± 36.1 ○ *P* values: Trabeculectomy vs. MIGS, 0.312; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.588; Trabeculectomy vs. Trabectome, 0.308; Trabeculectomy vs. 2x iStent Inject, 0.533 **QoL – Driving** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 76.2 ± 24.6; 42.5 ± 45.3; 65.0 ± 36.0; 54.5 ± 39.8 ○ *P* values: Trabeculectomy vs. MIGS, 0.421; Trabeculectomy vs. Trabectome vs. 2x iStent		

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	Inject, 0.143; Trabeculectomy vs. Trabectome, 0.138; Trabeculectomy vs. 2x iStent Inject, 0.537 **QoL – Colour vision** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 94.1 ± 13.1; 85.5 ± 26.7; 91.5 ± 18.6; 81.2 ± 28.7 ○ *P* values: Trabeculectomy vs. MIGS, 0.053; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.102; Trabeculectomy vs. Trabectome, 0.031; Trabeculectomy vs. 2x iStent Inject, 0.419 **QoL – Peripheral vision** at 6 mo post-operative (scale from 0 to 100), mean ± SD: • 72.0 ± 27.9; 67.1 ± 30.1; 70.5 ± 28.4; 57.2 ± 33.3 ○ *P* values: Trabeculectomy vs. MIGS, 0.089; Trabeculectomy vs. Trabectome vs. 2x iStent Inject, 0.194; Trabeculectomy vs. Trabectome, 0.069; Trabeculectomy vs. 2x iStent Inject, 0.351 **Safety** None		
Jea et al. 2012[64]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, Trabectome and Trabeculectomy, respectively, *P* values for between-group comparisons: • baseline: 28.1 ± 8.6; 26.3 ± 10.9, *P* = 0.190 • 1 mo: 19.8 ± 7.5; 10.4 ± 5.9, *P* < 0.001 • 3 mo: 18.2 ± 6.0; 12.0 ± 6.7, *P* < 0.001 • 6 mo: 18.3 ± 5.6; 11.3 ± 4.8, *P* < 0.001 • 12 mo: 17.4 ± 5.9; 12.2 ± 5.4, *P* < 0.001 • 18 mo: 17.0 ± 4.6; 12.0 ± 5.1, *P* < 0.001 • 24 mo: 15.9 ± 4.5, 43.5% reduction from baseline; 10.2 ± 4.1; 61.3% reduction from baseline, *P* < 0.001 • 30 mo: 16.6 ± 7.7; 10.0 ± 3.6, *P* = 0.001 **Medications** (number), mean ± SD, Trabectome and Trabeculectomy, respectively, *P* values for between-group comparisons: • Baseline: 3.3 ± 1.3; 3.4 ± 1.0, *P* = 0.289 • 1 mo: 2.6 ± 1.4; 0.4 ± 1.0, *P* < 0.001 • 3 mo: 2.8 ± 1.4; 0.4 ± 0.8, *P* < 0.001 • 6 mo: 2.4 ± 1.4; 0.8 ± 1.3, *P* < 0.001	• IOP and number of medications tended to be reduced from baseline in both groups, but this was not tested statistically • IOP and number of medications were not different between groups at baseline but were significantly lower in the Trabeculectomy vs. Trabectome group at all follow-up time points • VA was not different from baseline at 12 mo or 24 mo in either group, but was significantly better in the Trabectome vs. Trabeculectomy group at all time points	*"Trabeculectomy had a lower absolute IOP at all time points and fewer antiglaucoma medications. Although trabeculectomy showed clear superiority to [Trabectome] with regard to effect on IOP, there was the opposite result with regard to complications,"* p. 41.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 12 mo: 1.8 ± 1.3; 0.7 ± 1.2, *P* < 0.001 • 18 mo: 2.0 ± 1.5; 0.8 ± 1.2, *P* < 0.001 • 24 mo: 2.2 ± 1.6; 0.5 ± 1.0, *P* < 0.001 • 30 mo: 2.3 ± 1.8; 0.4 ± 1.0, *P* < 0.001 **VA (LogMAR),** mean ± SD, Trabectome and Trabeculectomy, respectively (*P* values for comparison with baseline unless otherwise stated): • baseline: 0.34 ± 0.40; 0.63 ± 0.82, between-group comparison *P* = 0.001 • 12 mo: 0.36 ± 0.26 (*P* = 0.753); 0.72 ± 0.81 (*P* = 0.462), between-group comparison *P* = 0.001 • 24 mo: 0.39 ± 0.31 (*P* = 0.551); 0.78 ± 0.66 (*P* = 0.356), between-group comparison *P* = 0.001 ○ There was no significant difference between groups in lines of Snellen VA lost (P = 0.055). ○ Significantly fewer patients in the Trabectome group (4.3%) lost ≥ 3 Snellen VA lines compared with patients in the Trabeculectomy group (12.7%; P = 0.028). **Safety** **Post-operative complications,** n (%), Trabectome and Trabeculectomy, respectively, *P* values for between-group comparisons where reported: • early hypotony: 0 (0%); 10 (9.8%) • persistent hypotony: 0 (0%); 5 (4.9%) • wound leak: 0 (0%); 12 (11.8%) • shallow anterior chamber: 0 (0%); 8 (7.8%) • choroidals: 0 (0%); 4 (3.9%) • early IOP spike: 4 (3.5%); 3 (2.9%) • hyphema: 115 (100.0%); 3 (2.9%) • cyclodialysis cleft: 1 (0.9%); 0 (0%) • cystoid macular edema: 0 (0%); 2 (2.0%) • conjunctival and tenon buttonhole: 0 (0%); 3 (2.9%) • corneal abrasion: 0 (0%); 1 (1.0%) • bullous keratopathy: 0 (0%); 1 (1.0%) • **Total number of patients with complications including hyphema:** 115 (100.0%); 39 (38.2%), *P* < 0.001 • **Total number of patients with complications excluding hyphema:** 5 (4.3%); 36 (35.3%), *P* < 0.001	• With the exception of hyphema, significantly more complications were reported in the Trabeculectomy group • More additional glaucoma procedures were performed after Trabectome than Trabeculectomy	

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	Additional glaucoma procedures, n (%), Trabectome and Trabeculectomy, respectively, *P* values for between-group comparisons where reported: • Trabeculectomy with MMC: 24 (20.8%); 0 (0%) • BGI: 18 (15.6%); 5 (4.9%) • repeated Trabectome: 4 (3.5%); 0 (0%) • combined Trabectome with phacoemulsification: 1 (0.9%); 0 (0%) • phacotrabeculectomy: 1 (0.9%); 0 (0%) • express shunt: 1 (0.9%); 0 (0%) • ECP: 1 (0.9%); 0 (0%) • needle revision of Trabeculectomy with MMC: 0 (0%); 3 (2.9%) • Trabectome: 0 (0%); 2 (2.0%) • SLT: 0 (0%); 1 (1.0%) • **Total number of patients with additional glaucoma procedures and surgeries**: 50 (43.5%); 11 (10.8%), *P* < 0.001		
Xen45 Vs. Trabeculectomy			
Schlenker et al. 2017[65]	**Clinical effectiveness** **IOP** (mm Hg) at last follow-up, median [IQR]: • last observation carried forward: Xen45, 13.0 [11.0 to 16.0]; Trabeculectomy, 13.0 [11.0 to 16.0], *P* = 0.98 • censoring for reoperation: Xen45, 13.0 [10.0 to 15.0]; Trabeculectomy, 13.0 [10.0 to 16.0], *P* = 0.32 **Medication use** (percentage of eyes) at 1 y follow-up: • crude: Xen45 (n = 111), 25.1%, 95% CI, 17.3 to 35.0; Trabeculotomy (n = 74), 36.0%, 95% CI 24.9 to 48.9; *P* = NR • Last observation carried forward: Xen45, 23.8%, 95% CI, 13.9 to 37.6; Trabeculotomy, 33.5%, 95% CI 20.2 to 50.0 **Medication use** (number) at last follow-up using last observation carried forward, median [IQR]: • Xen45, 0.0 [0.0 to 1.0]; Trabeculectomy, 0.0 [0.0 to 0.0], *P* = NR **BCVA** (logMAR) at last follow-up or before reoperation, median [IQR]: • Xen45, 0.2 [0.1 to 0.5]; Trabeculectomy, 0.3 [0.1 to 0.5], *P* = 0.24 **Characteristics associated with surgical failure:** • The following were not associated with surgical failure: Xen45 vs. Trabeculectomy, age < 75	• IOP, medication use, and BCVA were similar between groups at follow-up • There tended to be more post-surgical interventions and complications in the Trabeculectomy group (but this was not tested statistically) • There tended to be more reoperations in the Xen45 group, but this did not reach statistical significance	*"There was no detectable difference in risk of failure and safety profiles between standalone ab interno [Xen45] with MMC and trabeculectomy with MMC,"* p. 1579.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	y, female, poor preoperative vision (VA of 0.4 logarithm of the minimum angle of resolution or worse), preoperative IOP > 21 mm Hg, moderate or advanced vs. mild disease based on visual field MD (–6 cut-off), pseudophakia, prior LPI, prior trabeculoplasty. **Effect Modification:** • Eyes with preoperative IOP > 21 mm Hg tended to do better with Xen45 relative to Trabeculectomy; HR, 0.70; 95% CI, 0.43 to 1.12; eyes with preoperative IOP ≤ 21 mm Hg tended to do better with Trabeculectomy relative to Xen45; HR, 1.78; 95% CI, 0.97 to 3.27; interaction between preoperative IOP and intervention, *P* = 0.016 • Eyes with preoperative BCVA of > 0.4 logMAR tended to do better with Xen45 relative to Trabeculectomy; HR, 0.38; 95% CI, 0.16 to 0.89; eyes with BCVA of ≤ 0.4 logMAR or worse tended to do better with Trabeculectomy relative to Xen45; HR, 1.33; 95% CI, 0.86 to 2.05; interaction between preoperative BCVA and intervention, *P* = 0.010 **Safety** **Post-operative interventions**, number, Xen45, Trabeculectomy (between-group comparison, *P* = NR): • needling: 80, 52 • laser suture lysis: not relevant for intervention, 84 • anterior-chamber reformation: 22, 13 • bleb repair/conjunctival suturing: 2, 10 • Iris sweep/synechiolysis: 3, 4 • YAG to implant/ostomy: 3, 2 • MMC injection: 2, 0 • Xen45 reposition: 2, not relevant for intervention • iridoplasty: 2, 0 • laser to ostomy: not relevant to intervention, 0 • bleb cautery: 1, 0 • **Total:** Xen45, 117; Trabeculectomy, 165 **Post-operative complications at > 1 mo**, number Xen45, Trabeculectomy (between-group comparison, *P* = NR): • leak/dehiscence: 3, 12 • hyphema: 2, 2 • vitreous hemorrhage: 2, 1 • choroidals or choroidal folds: 1, 2		

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• hypotony maculopathy: 2, 1 • uveitis: 2, 1 • corneal decompensation: 0, 1 • macular edema: 0, 3 • diplopia: 0, 0 • iris incarceration: not relevant for intervention, 2 • blocked Xen45: 1, not relevant for intervention • exposed Xen45: 1, not relevant for intervention • Xen45 – iris touch: 2, not relevant for intervention • shallow anterior chamber: 0, 2 • dellen: 2, 0 • serious complication (any time): ○ retinal detachment: 0, 0 ○ angle closure: 0, 0 ○ suprachoroidal hemorrhage: 0, 0 ○ malignant glaucoma: 4, 2 ○ blebitis: 0, 1 ○ endophthalmitis: 0, 0 ○ no LP: 0, 0 • **Total:** Xen45, 22; Trabeculectomy, 30 **Reoperations,** n (%), Xen45, Trabeculectomy: • Xen45: 7 (3.8%), 1 (0.6%) • Baerveldt tube shunt: 6 (3.2%), 2 (1.2%) • cyclophotocoagulation: 1 (0.5%), 3 (1.8%) • Ahmed valve: 1 (0.5%), 1 (0.6%) • Trabeculectomy: 2 (1.1%), 0 (0.0%) • bleb revision: 1 (0.5%), 1 (0.6%) • microshunt: 1 (0.5%), 0 (0.0%) • suprachoroidal stent: 0 (0.0%), 1 (0.6%) • trabecular bypass stents: 0 (0.0%), 1 (0.6%) • **Total:** Xen45, 19 (10.3%); Trabeculectomy, 9 (5.3%), between-group comparison, *P* = 0.11 • Other laser/surgery: ○ Phaco: 11 (5.9%), 16 (9.5%) ○ LPI: 1 (0.5%), 1 (0.6%) ○ Trabeculoplasty: 1 (0.5%), 0 (0.0%)		

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	○ retinal surgery: 0 (0.0%), 1 (0.6%) ○ corneal surgery: 0 (0.0%), 0 (0.0%)		
Research Questions 3 and 4			
MIGS + Cataract Surgery Vs. Cataract Surgery Alone			
ECP + Phaco Vs. Phaco Alone			
Kang et al. 2017[72]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, ECP + Phaco and Phaco, respectively (*P* values for comparison with baseline, where reported): • baseline: 20.4 ± 6.25; NR • follow-up: 14.4 ± 3.95 (*P* = 0.0000004); NR **Glaucoma medications** (number), mean ± SD, ECP + Phaco and Phaco, respectively (*P* values for comparison with baseline, where reported): • baseline: 2.7 ± 0.9; NR • follow-up: 1.9 ± 1.3 (*P* = 0.001); NR **VA** at follow-up (range 6 wk to 2 y 6 mo), number of eyes (%) compared with preoperative, ECP + Phaco and Phaco, respectively; no statistical comparisons: • improved: 47 (75.8); 54 (87.1) • same: 12 (19.4); 7 (11.3) • worsened: 3 (4.8); 1 (1.61) **Safety** **Post-operative complications** in ECP + Phaco (n = 7 eyes; 11.3%): • four eyes developed uveitis; more intensive topical steroids were required; all eyes had visual acuities of 6/6 at last follow-up • one eye developed fibrinous uveitis with a pupillary membrane; YAG laser required • one eye required intracameral tissue plasminogen activator injection with synechiolysis at 1 mo post-operative; BCVA of hand movement was unchanged • one eye, with existing ocular cicatricial pemphigoid and bilateral juxtafoveal telangiectasia, developed macular oedema **Post-operative complications** in the Phaco only group: None • No cases of hypotony, lens subluxation or dislocation, or requirement of capsular tension ring in either group	• IOP and number of medications were reduced in ECP + Phaco but not reported in Phaco alone • VA was unchanged or improved from baseline in most patients • The ECP + Phaco group had more complications than those with Phaco alone (no complications)	*"[ECP + Phaco] should be considered as an effective, safe and predictable surgical treatment option for glaucoma patients with co-existing cataract,"* p. 1311.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
Perez Bartolome et al. 2017[73]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, ECP + Phaco and Phaco respectively (*P* values for comparison with baseline unless otherwise stated): • baseline (as reported in study Table 1): 21.48 ± 5.41; 18.43 ± 3.68; between-group comparison, *P* = 0.005 • baseline (as reported in study Table 2): 21.45 ± 5.56; 18.43 ± 3.68; between-group comparison, *P* = NR • 1 d: 17.88 ± 7.18 (*P* < 0.001); 12.03 ± 2.43 (*P* < 0.001) • 7 d: 14.42 ± 4.78 (*P* < 0.001); 11.86 ± 2.58 (*P* = 0.024) • 1 mo: 14.87 ± 4.4 (*P* < 0.001); 14.56 ± 1.56 (*P* < 0.001) • 3 mo: 15.17 ± 3.95 (*P* < 0.001); 17.5 ± 2.31 (*P* = 0.204) • 6 mo: 15.73 ± 3.88 (*P* < 0.001); 16.7 ± 1.91 (*P* = 0.021) • 12 mo: 16.8 ± 3.81 (*P* < 0.001); 16.6 ± 1.63 (*P* = 0.013); *P* value for between-group comparison, *P* = 0.721 **IOP reduction from baseline** at 1 y, mean ± SD, ECP + Phaco and Phaco, respectively (*P* values for between-group comparisons): • absolute IOP (mm Hg): 4.5 ± 5.13; 1.83 ± 3.61; *P* = 0.007 • % reduction in IOP: 21.56 ± 10.4; 9.9 ± 7.5; *P* = 0.003 **Medications** (number), mean ± SD, ECP + Phaco and Phaco, respectively (*P* values for comparison with baseline unless otherwise stated): • baseline (as reported in study Table 1): 2.62 ± 0.82; 1.2 ± 0.8; between-group comparison, *P* < 0.001 • baseline (as reported in study Table 2): 2.61 ± 0.83; 1.2 ± 0.805; between-group comparison, *P* = NR • 1 d: 2.55 ± 0.89 (*P* = 0.09); 1.13 ± 0.63 (*P* = 0.563) • 7 d: 2.33 ± 0.85 (*P* < 0.001); 1 ± 0.74 (*P* = 0.083) • 1 mo: 2.4 ± 0.87 (*P* = 0.005); 0.93 ± 0.78 (*P* = 0.058) • 3 mo: 2.3 ± 0.87 (*P* = 0.003); 1.03 ± 0.66 (*P* = 0.057) • 6 mo: 2.07 ± 0.91 (*P* < 0.001); 1.06 ± 0.58 (*P* = 0.255) • 12 mo: 1.89 ± 0.98 (*P* < 0.001); 0.96 ± 0.61 (*P* = 0.032) **Medication-free patients,** n (%): ECP + Phaco, 11 (15.94%); Phaco, 2 (6.66%), *P* = NR	• Disease severity at baseline was higher in the ECP + Phaco vs. Phaco groups • Absolute IOP was significantly reduced from baseline in both groups at 1 d to 12 mo follow-up, but was not different between groups; the mean IOP reduction was significantly greater in the ECP + Phaco group (but IOP was higher at baseline in this group) • The number of medications was significantly reduced from baseline in the ECP + Phaco group from 7 d to 12 mo follow-up, and in the Phaco group at 12 mo follow-up only; the reduction in the number of medications used at 12 mo was greater in the ECP + Phaco group (but the number of medications was higher at baseline in this group) • VA was significantly reduced from baseline at 1 d follow-up in ECP + Phaco group only, but was significantly increased from baseline in both groups at 1 mo to	*"…[ECP + Phaco] is both safe and effective as surgical management for cataract and glaucoma. Compared to phacoemulsification alone, [ECP + Phaco] results in greater IOP reduction and reduced dependence on glaucoma medication in patients with moderate and advanced POAG. Despite [ECP + Phaco] having a higher number of complications, these were easily treated and did not limit the improvement in VA,"* p. 6.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	Medication reduction from baseline at 1 y, mean ± SD, ECP + Phaco and Phaco, respectively (*P* values for between-group comparison): • absolute medication (number): 0.73 ± 0.71; 0.23 ± 0.56; *P* = 0.001 • % reduction in number of medications: 26.68 ± 12.2; 21.3 ± 8.1; *P* = 0.032 **VA** (logMAR), mean ± SD, ECP + Phaco and Phaco, respectively (*P* values for comparison with baseline unless otherwise stated): • baseline (as reported in study Table 1): 0.33 ± 0.25; 0.44 ± 0.3; between-group comparison, *P* = 0.079 • baseline (as reported in study Table 2): 0.33 ± 0.25; 0.42 ± 0.2; between-group comparison, *P* = NR • 1 d: 0.61 ± 0.29 (*P* < 0.001); 0.15 ± 0.11 (*P* < 0.001) • 7 d: 0.31 ± 0.19 (*P* = 0.635); 0.11 ± 0.05 (*P* < 0.001) • 1 mo: 0.12 ± 0.08 (*P* < 0.001); 0.11 ± 0.04 (*P* < 0.001) • 3 mo: 0.1 ± 0.05 (*P* < 0.001); 0.12 ± 0.05 (*P* < 0.001) • 6 mo: 0.08 ± 0.07 (*P* < 0.001); 0.08 ± 0.04 (*P* < 0.001) • 12 mo: 0.07 ± 0.05 (*P* < 0.001); 0.09 ± 0.02 (*P* < 0.001) **Subgroup Analysis — within ECP + Phaco group, patients without vs. with previous surgeries, respectively:** • IOP reduction (mm Hg): 5.2 ± 5.3; 4.12 ± 5.21, *P* = 0.12 • % IOP reduction (%): 22.13 ± 11.5; 19.52 ± 9.3, *P* = 0.09 • reduction in medications (number): 0.79 ± 0.6; 0.71 ± 0.83, *P* = 0.11 • % reduction in number of medications (%): 27.72 ± 10.5; 25.91 ± 14.32, *P* = 0.085 **Safety** **Complications,** n (%), between-group difference, *P* = 0.047; ECP + Phaco and Phaco, respectively: • none: 52 (75.36%); 27 (90%) • raised IOP: 5 (7.24%); 1 (3.33%) • persistent (≥ 6 wk) post-operative uveitis: 6 (8.69%); 1 (3.33%) • macular edema: 4 (5.79%); 1 (3.33%) • choroidal detachment: 1 (1.45%); 0 (0%) • retinal detachment: 1 (1.45%); 0 (0%)	12 mo follow-up • There were more post-operative complications in the ECP + Phaco vs. the Phaco group	

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
Sheybani et al. 2015[74]	**Clinical effectiveness** **IOP** (mm Hg) averaged over 3 visits, mean ± SD, ECP + Phaco and Phaco, respectively (*P* values for between-group comparisons unless otherwise stated): • baseline: 17.6 ± 9.0; 16.1 ± 4.2, *P* = 0.083 • at follow-up (range 1 to 43.4 mo): 14.4 ± 3.65 (compared with baseline, *P* = 0.003); 14.1 ± 3.83 (compared with baseline, *P* = 0.007), *P* = 0.378 **Medications** (number), mean (range), ECP + Phaco and Phaco, respectively: • baseline: 2.0 (0 to 3); 0.4 (0 to 3), *P* < 0.001 • at follow-up (range 1 to 43.4 mo): 1.51 (0 to 3) (compared with baseline, *P* < 0.001); 0.38 (0 to 3) (compared with baseline, *P* = 0.434), *P* < 0.001 **BCVA** (logMAR), mean, ECP + Phaco and Phaco, respectively: • baseline: 0.382; 0.358, *P* = 0.608 • 1 mo: 0.200; 0.144, *P* = 0.125 **Safety** None	• IOP was reduced from baseline in both groups and was not different between groups at follow-up; however, mean follow-up was longer in the ECP + Phaco vs. Phaco group (7.4 mo vs. 2.1 mo) • The number of medications was reduced from baseline at follow-up only in the ECP + Phaco group, but was significantly lower in the Phaco vs. ECP + Phaco group at both time points • BCVA was not different between groups at baseline or follow-up	*"Only the [ECP + Phaco] group had a statistically significant decrease in the number of ocular hypotensive medication[s] used between preoperative and postoperative visits (*p < *0.05). Both groups had a significant decrease in IOP between preoperative and postoperative visits (*p < *0.05), with a larger decrease observed in the [ECP + Phaco] group (18.2%) compared with the cataract alone group (12.4%),"* p. 199.
Siegel et al. 2015[75]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, ECP + Phaco and Phaco, respectively (*P* values for between-group comparisons): • baseline: 17.2 ± 4.8; 17.7 ± 4.4, *P* = 0.52 • 6 mo: 14.7 ± 3.5; 16.0 ± 3.3, *P* = 0.06 • 12 mo: 14.7 ± 3.5; 16.2 ± 3.4, *P* = 0.17 • 18 mo: 14.9 ± 3.1; 14.4 ± 3.2, *P* = 0.39 • 24 mo: 15.0 ± 3.1; 14.1 ± 2.9, *P* = 0.08 • 30 mo: 14.8 ± 3.8; 13.5 ± 2.5, *P* = 0.11 • 36 mo: 14.6 ± 3.1; 15.5 ± 3.6, *P* = 0.34 ○ In both groups, there was a main effect of time, *P* < 0.001 **IOP reduction from baseline (%)**, mean ± SD, ECP + Phaco and Phaco, respectively (P values NR): • 1 mo: 4.5 ± 2.2; 2.2 ± 4.3 • 6 mo: 11.5 ± 1.8; 3.9 ± 4.0	• IOP was reduced from baseline in both groups, but mean IOP was not different between groups at any time point • The number of medications was reduced from baseline in both groups, and was significantly lower in the ECP + Phaco vs. Phaco group at baseline (possibly; inconsistent *P* values reported) and all follow-up time points • VA tended to increase from baseline to 36 mo	*"Combined [ECP + Phaco] effectively lowers or maintains intraocular pressure and results in ocular hypertensive medication reduction up to 36 months when compared with Phaco alone. Therefore, [ECP + Phaco] may help to increase medication compliance and reduce glaucoma progression in mild to moderate glaucoma,"* p. 531-532.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 12 mo: 10.9 ± 1.6; 4.4 ± 4.1 • 18 mo: 9.9 ± 1.6; 15.1 ± 3.3 • 24 mo: 10.3 ± 1.5; 15.2 ± 4.4 • 30 mo: 14.8 ± 1.3; 17.2 ± 4.3 • 36 mo: 12.6 ± 1.4; 7.1 ± 5.9 **Medications** (number), mean ± SD, ECP + Phaco and Phaco, respectively (*P* values for between-group comparisons): • baseline: 1.3 ± 0.6; 1.5 ± 0.7, reported as *P* = 0.22 in study Table 1 and *P* = 0.02 in study Table 2 • 6 mo: 0.1 ± 0.4; 1.3 ± 0.8, *P* <0.001 • 12 mo: 0.2 ± 0.6; 1.4 ± 1.0, *P* <0.001 • 18 mo: 0.2 ± 0.5; 1.4 ± 0.9, *P* <0.001 • 24 mo: 0.2 ± 0.5; 1.3 ± 0.9, *P* <0.001 • 30 mo: 0.2 ± 0.6; 1.3 ± 0.9, *P* <0.001 • 36 mo: 0.2 ± 0.59; 1.3 ± 0.61, *P* < 0.001 ○ In both groups, there was a main effect of time, *P* < 0.001 **VA** (Snellen), median, ECP + Phaco and Phaco, respectively (*P* values for between-group comparisons): • baseline: 20/50; 20/60, *P* = 0.10 • 36 mo: 20/30; 20/30, *P* = 0.07 **Safety** **Surgical complications, n:** • ECP + Phaco*:* Secondary glaucoma procedure required, 7; CME development, 4; retinal detachments, 2; penetrating keratoplasty required, 1 • Phaco*:* CME development, 1 **IOP spikes** were only reported for the complete sample and not for the individual groups. Overall, 90.03% of patients had no IOP spikes; 8.04% had 1 IOP spike; and 1.91% had 2 IOP spikes.	follow-up in both groups, but this was not tested statistically, and VA was not significantly different between groups at either time point • Full and qualified success were both significantly greater in the ECP + Phaco group vs. the Phaco group • There were few complications overall, and there tended to be more complications in the ECP + Phaco vs. Phaco group, but this was not tested statistically	
Francis et al. 2014[84]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, ECP + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • Baseline: 18.1 ± 3.0; 18.1 ± 3.0, *P* = 1.00	• IOP was significantly reduced from baseline in both groups at 36 mo, but IOP was significantly	*"[ECP] added to cataract extraction resulted in greater reduction in IOP and glaucoma medications than cataract*

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 6 mo: 15.6 ± 2.5; 17.9 ± 3.5, *P* < 0.001 • 12 mo: 16.0 ± 2.8; 17.5 ± 3.6, *P* = 0.004 • 24 mo: 16.0 ± 3.3; 17.3 ± 3.2, *P* = 0.01 • 36 mo: 15.4 ± 2.5; 17.2 ± 3.0, *P* = 0.003 **IOP change from baseline** (%), mean ± SD, ECP + Phaco and Phaco alone, respectively (*P* values for comparison with baseline unless otherwise stated): • 6 mo: 12.4 ± 16.7 (P < 0.001); 0.7 ± 13.1 (P = NS), between-group *P* < 0.001 • 12 mo: 10.2 ± 17.1 (P < 0.001); 2.7 ±16.2 (P = NS), between-group *P* = 0.005 • 24 mo: 10.1 ± 18.7 (P < 0.001); 0.8 ± 12 (P = NS), between-group *P* = 0.02 • 36 mo: 13.6 ± 15.1 (P < 0.001); 5.1 ± 10.4 (P = 0.01), between-group *P* = 0.003 **Medications** (number), mean ± SD, ECP + Phaco and Phaco alone, respectively (*P* values between-group comparisons): • baseline: 1.5 ± 0.8; 2.4 ± 1.0, *P* < 0.001 • 6 mo: 0.3 ± 0.7; 1.5 ± 1.2, *P* < 0.001 • 12 mo: 0.4 ± 0.7; 1.8 ± 1.2, *P* < 0.001 • 24 mo: 0.4 ± 0.7; 2.0 ± 1.0, *P* < 0.001 • 36 mo: 0.4 ± 0.7; 2.3 ± 1.0, *P* < 0.001 **Reduction in number of medications from baseline** (n), mean ± SD, ECP + Phaco and Phaco alone, respectively (*P* values for comparison with baseline unless otherwise stated): • 6 mo: –1.1 ± 0.8 (*P* < 0.001); –0.9 ± 1.2 (*P* < 0.001), between-group *P* = 0.24 • 12 mo: –1.0 ± 0.9 (*P* < 0.001); –0.6 ± 0.9 (*P* < 0.001), between-group *P* = 0.006 • 24 mo: –1.1 ± 0.9 (*P* < 0.001); –0.4 ± 0.8 (*P* < 0.001), between-group *P* < 0.001 • 36 mo: –1.0 ± 0.9 (*P* < 0.001); –0.1 ± 0.8 (*P* = NS), between-group *P* < 0.001 **Safety** **Adverse events,** n, (%), ECP + Phaco and Phaco alone, respectively (*P* values NR): • anterior-chamber hemorrhage: 2 (2.5%), 0 (0%) • significant inflammation: 0 (0%), 2 (2.5%) • CME: 0 (0%), 3 (3.8%) • hemorrhage: 0 (0%), 1 (1.3%)	lower in ECP + Phaco vs. Phaco alone at all follow-up time points • The number of medications was significantly reduced from baseline at all follow-up time points in both groups (with the exception of 36 mo in Phaco alone), but was significantly lower in the ECP + Phaco group vs. the Phaco alone group at all time points • Adverse events were similar between groups, but this was not tested statistically	*extraction alone over a 3-year period,"* p. 1319. *"The data indicate that combining ECP with [Phaco does] not substantially [add] to the risks of [Phaco] alone,"* p. 1319.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
1x or 2x iStent + Phaco Vs. Phaco Alone			
El Wardani et al. 2015[76]	**Clinical effectiveness** Note: In this study, different numerical values were reported in the abstract, text, and tables; all distinct values are presented here (e.g., value 1 *or* value 2). **IOP** (mm Hg), mean, iStent + Phaco, 2x iStent + Phaco, and Phaco alone, respectively (*P* values for comparison with baseline where available): • baseline: 16.7 *or* 17.5; 17.0; 16.3 • 1 d: 18.2; 16.1; 17.0 • 1 wk: 16.7; 16.4; 16.4 • 1 mo: 13.9; 15.5; 14.5 • 3 mo: 15.0; 13.8; 14.0 • 6 mo: 15.1 *or* 14.7 (*P* < 0.16 *or* *P* = 0.01); 13.8 *or* 14.4 (P = 0.05 *or* *P* = 0.07); 13.9 *or* 14.2 (*P* < 0.01) ○ *"There was no significant change between groups at any time point"* p. 444 (*P* values NR) **Medications** (number), mean, iStent + Phaco, 2x iStent + Phaco, and Phaco alone, respectively (*P* values for comparison with baseline where available): • baseline: 1.8 *or* 2.5; 2.1; 1.9 • 1 d: 0.6; 0.3; 1.9 • 1 wk: 1.0; 1.3; 1.6 • 1 mo: 1.0; 1.7; 1.5 • 3 mo: 0.8; 1.0; 1.7 • 6 mo: 1.0 *or* 0.8 (*P* = NR *or* *P* = 0.04); 1.0 *or* 1.2 (*P* < 0.01 *or* *P* = NR); 1.6 *or* 1.8 (*P* = 0.12 *or* *P* = NR) ○ *"There was a significant decrease in medications in both iStent groups compared with phacoemulsification alone"* p. 445 (*P* values NR) **VA** (units not specified), median, iStent + Phaco, 2x iStent + Phaco, and Phaco alone respectively: • baseline: 0.4; 0.5; 0.3 • other time points: NR *"There was a significant improvement of visual acuity in all groups." (P* = NR) **Safety** None	• Because of inconsistency in reporting, interpretation of findings is unclear • IOP may have been unchanged *or* significantly reduced from baseline at 6 mo in the iStent + Phaco and 2x iStent + Phaco groups, and appeared to have been significantly reduced from baseline at 6 mo in the Phaco alone group, with no significant between-group difference in IOP at any time point • The number of medications may have been reduced from baseline in the iStent + Phaco and 2x iStent + Phaco, but not Phaco alone, groups	*"iStent implantation resulted in similar IOP reduction to phacoemulsification alone but achieved a significantly greater reduction in glaucoma medications. This may improve compliance and quality of life, and reduce health care costs in patients with early to moderate glaucoma,"* p. 442.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
Fea et al. 2015[66] and Fea 2010[67]	**Clinical effectiveness** **IOP** (medicated unless otherwise stated; mm Hg), mean ± SD, iStent + Phaco and Phaco, respectively (*P* values for between-group comparisons unless otherwise stated): • baseline: 17.9 ± 2.6; 17.3 ± 3.0, *P* = 0.512 • 12 mo: 14.7 ± 1.3; 15.6 ± 1.1, *P* = NR • 12 mo (after medication washout): 16.1 ± 2; 18.4 ± 3.1, *P* = 0.05 • 15 mo: 14.8 ± 1.2; 15.7 ± 1.1, *P* = 0.031 • 16 mo (after 1 mo medication washout): 16.6 ± 3.1; 19.2 ± 3.5, *P* = 0.042 • 48 mo: 15.9 ± 2.3; 17 ± 2.5, *P* = NS • 48 mo (after medication washout): 17.5 ± 2.3 (compared with before washout *P* = 0.14); 20.4 ± 3.2 (compared with before washout *P* = 0.04) **Reduction in IOP** from baseline (mm Hg), mean ± SD where reported, iStent + Phaco and Phaco, respectively: • 15 mo: 3.2 ± 3.0; 1.6 ± 3.2, *P* = 0.177 • 48 mo (after medication washout): 0.3; 3.7; between-group difference 14.2% (*P* = 0.02) **Medications** (number), mean ± SD, iStent + Phaco and Phaco, respectively (*P* values for between-group comparisons unless otherwise stated): • baseline: 2.0 ± 0.9; 1.9 ± 0.7, *P* = NR • 12 mo: 0.4 ± 0.7 (compared with baseline *P* = 0.003); 1 ± 1 (compared with baseline *P* = 0.01), *P* = NR • 15 mo: 0.4 ± 0.7; 1.3 ± 1.0, *P* = 0.007 • 48 mo: 0.5 ± 0.8 (compared with baseline *P* = 0.005); 0.9 ± 1 (compared with baseline *P* = 0.01); *P* = NS **Number of patients requiring no medication at 15 mo,** n (%), iStent + Phaco and Phaco, respectively: • 8 (67%); 5 (24%), *P* = 0.027 **Safety** **Adverse events, n:** • iStent + Phaco: Stent malposition, 2 • Phaco: Ruptured capsule, 1	• Absolute IOP was significantly lower at both medicated (15 mo) and unmedicated (16 mo) follow-up in the iStent + Phaco vs. Phaco groups, but was not different between groups at 48 mo follow-up • Medication use was significantly lower in the iStent + Phaco vs. Phaco groups at 15 mo but not 48 mo follow-up	*"Phacoemulsification with stent implantation was more effective in controlling IOP than phacoemulsification alone; the safety profiles were similar,"* p. 407.[67] *"In conclusion, most patients having a combined* [iStent + Phaco] *maintained IOP target levels without medication through 15 months postoperatively. Conversely, the majority of patients having only* [Phaco] *reached the target IOP only with the addition of medications. Therefore, the stent reduced the need for medications postoperatively…"* p. 411.[67] *"[P]atients having* [iStent + Phaco] *maintained low IOP levels after 48 months of follow-up.* [Phaco] *alone showed a loss of efficacy in controlling IOP over time. Both treatments reduced the number of ocular hypotensive medications prescribed,"* p. 4.[66]

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
Craven et al. 2012[68] and Samuelson et al. 2011[34]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, iStent + Phaco and Phaco alone, respectively, *P* values for between-group comparisons where available: • screening (medicated): 18.7 ± 3.3; 18.0 ± 3.0 • baseline (unmedicated): 25.2 ± 3.5; 25.5 ± 3.7, *P* = 0.517 • 12 mo (consistent cohort): 17.0 ± 2.8; 17.0 ± 3.1, *P* = NR • 24 mo (consistent cohort): 17.1 ± 2.9; 17.8 ± 3.3, *P* = NR **Reduction in IOP from unmedicated screening** (mm Hg), iStent + Phaco and Phaco alone, respectively, *P* values NR: • 12 mo: 8.4 ± 3.6; 8.5 ± 4.3 • 24 mo: 8.4 ± NR; 7.5 ± NR **Reduction in IOP from medicated baseline** (mm Hg), iStent + Phaco and Phaco alone, respectively, *P* value NR: • 12 mo: 1.5 ± 3.0; 1.0 ± 3.3 **Medications** (number), mean ± SD, iStent + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • screening: 1.5 ± 0.7; 1.5 ± 0.6, *P* = 0.451 • 12 mo (consistent cohort): 0.2 ± 0.6; 0.4 ± 0.7, *P* = 0.016 • 24 mo (consistent cohort): 0.3 ± 0.6; 0.5 ± 0.7, *P* = NS **Reduction in medications from screening** (number), iStent + Phaco and Phaco alone, respectively, *P* value for between-group comparison: • 12 mo: 1.4 ± 0.8; 1.0 ± 0.8, *P* = 0.005 **CDVA,** n (%), iStent + Phaco and Phaco alone, respectively, *P* values NR: Baseline: • 20/40 or better: 49 (45%); 53 (44%) 12 mo: • 99 (94%); 101 (90%) 24 mo: • 20/40 or better: NR (93%); NR (91%) • 20/32 or better: NR (83%); NR (82%) • 20/25 or better: NR (63%); NR (67%)	• At 12 and 24 mo follow-up, absolute mean IOP tended to be similar between groups (statistical comparison not reported) • The number of medications was significantly lower in the iStent + Phaco vs. the Phaco alone group at 12 months, but was not different between groups at 24 months • CDVA was similar between groups, but this was not tested statistically • The VF was similar between groups at baseline and 24 mo follow-up • Complications were similar between groups, but this was not tested statistically	*"A significantly higher proportion of patients [with iStent + Phaco] had IOP control on no medication through 2 years postoperatively compared with patients having [Phaco] alone. Both groups had a similar favorable long-term safety profile,"* p. 1345.[68] *"In conclusion, the implantation of the stent in patients undergoing cataract surgery provided clinically and statistically significant improvements in the management of elevated IOP compared with [Phaco] alone, with a favorable safety profile and clinically significant reductions in IOP and medication,"* p. 466.[34] *"Although mean reduction in IOP appeared similar in both groups, a substantially higher level of medication was used in the [Phaco alone] group to maintain this similar IOP level,"* p. 463.[34]

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 20/20 or better: NR (34%); NR (32%) **VF mean deviation (dB),** mean ± SD, iStent + Phaco and Phaco alone, respectively, *P* values for between-group comparisons: • baseline: –3.75 ± 3.03; –3.74 ± 3.86, *P* = 0.983 • 24 mo: –3.22 ± 3.01; –3.16 ± 3.66, *P* = NS **VF PSD (dB),** mean ± SD, iStent + Phaco and Phaco alone, respectively, *P* values for between-group comparisons: • baseline: 2.89 ± 1.79; 2.79 ± 1.90, *P* = NR • 24 mo: 3.39 ± 2.29; 3.17 ± 2.51, *P* = NS **Safety** **Intraoperative complications,** n (%), iStent + Phaco and Phaco alone, respectively, *P* values NR: Cataract surgery complications: • vitreous removal/vitrectomy: 5 (4.3%); 3 (2.6%) • IOP removal and replacement (torn IOL haptic): 0 (0%); 1 (0.9%) Stent implantation complications: • unsuccessful stent implantation: 1 (0.9%); NA • intraoperative stent removal and replacement: 1 (0.9%); NA • stent malposition: 1 (0.9%); NA • iris touch: 8 (7.0%); NA • endothelial touch: 1 (0.9%); NA **Post-operative complications ≥ 2% at 12 mo,** n (%), iStent + Phaco and Phaco alone, respectively, *P* values NR: • anticipated early post-operative event[1]: 14 (13%); 15 (12%) • stent obstruction by iris, vitreous, fibrous overgrowth, fibrin, blood, and so forth: 4 (4%); 0 (0%) • posterior capsular opacification: 3 (3%); 8 (7%) • stent malposition: 3 (3%); 0 (0%) • subconjunctival hemorrhage: 2 (2%); 2 (2%) • elevated IOP, other: 2 (2%); 1 (1%) • epiretinal membrane: 2 (2%); 1 (1%) • iris atrophy: 2 (2%); 0 (0%)		

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• blurry vision or visual disturbance: 1 (1%); 6 (5%) • iritis: 1 (1%); 6 (5%) • dry eye: 1 (1%); 2 (2%) • elevated IOP requiring treatment with oral or intravenous medications or surgical interventions: 1 (1%); 2 (2%) • macular edema: 1 (1%); 2 (2%) • foreign body sensation: 0 (0%); 3 (2%) • allergic conjunctivitis: 0 (0%); 2 (2%) • mild pain: 0 (0%); 2 (2%) • rebound inflammation from tapering steroids: 0 (0%); 2 (2%) **Post-operative complications ≥ 3% at 24 mo,** n (%), iStent + Phaco and Phaco alone, respectively, *P* values NR: • anticipated early post-operative event:[a] 20 (17.2%); 22 (18.8%) • posterior capsule opacification: 7 (6.0%); 12 (10.3%) • elevated IOP: 5 (4.3%); 8 (6.8%) ◦ elevated IOP — other: 4 (3.4%); 5 (4.3%) ◦ elevated IOP requiring treatment with oral or intravenous medications or with surgical intervention: 1 (0.9%); 3 (2.6%) • stent obstruction: 5 (4.3%); NA • blurry vision or visual disturbance: 4 (3.4%); 8 (6.8%) • stent malposition: 3 (2.6%); NA • iritis: 1 (0.9%); 6 (5.1%) • conjunctival irritation due to hypotensive medication: 1 (0.9%); 3 (2.6) • disc hemorrhage: 1 (0.9%); 3 (2.6%) **Secondary surgical interventions at 12 mo,** n *(%),* iStent + Phaco and Phaco alone, respectively, *P* values NR: • paracentesis: 31 (28%); 33 (27%) • Nd:YAG laser capsulotomy: 4 (4%); 7 (6%) • stent repositioning: 3 (3%); NA • punctal cautery/punctual plugs: 1 (1%); 2 (2%) • focal argon laser photocoagulation: 1 (1%); 0 (0%) • Nd:YAG laser for stent obstruction: 1 (1%); NA • stent removal and replacement: 1 (1%); NA • trabeculoplasty: 0 (0%); 2 (2%)		

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• deep sclerectomy/sclerostomy: 0 (0%); 1 (1%) • IOL removal and replacement: 0 (0%); 1 (1%) • LASIK: 0 (0%); 1 (1%) • pupilloplasty: 0 (0%); 1 (1%) • vitrectomy: 0 (0%); 1 (1%) • wound resuture due to wound leak: 0 (0%); 1 (1%) **Secondary surgical interventions at 24 mo**, n (%), iStent + Phaco and Phaco alone, respectively, *P* values NR: • stent repositioning: 3 (2.6%); NA • stent removal and replacement: 1 (0.9%); NA • Nd:YAG laser for stent obstruction: 1 (0.9%); NA • trabeculoplasty: 1 (0.9%); 2 (1.7%) • focal argon laser photocoagulation: 1 (0.9%); 0 (0%) • deep sclerectomy/sclerostomy: 0 (0%); 1 (0.9%) • IOL removal and replacement: 0 (0%); 1 (0.9%) • LASIK: 0 (0%); 1 (0.9%) • pupilloplasty: 0 (0%); 1 (0.9%) • vitrectomy: 0 (0%); 1 (0.9%) • wound resuture due to wound leak: 0 (0%); 1 (0.9%) • **Total patients (some had > 1 intervention):** 5 (4.3%); 6 (5.1%) [a] "Anticipated early post-operative events" included early post-operative corneal edema, anterior-chamber cells, corneal abrasion, discomfort, subconjunctival hemorrhage, blurry vision, and floaters as anticipated in the early period after cataract surgery.		
Fernandez-Barrientos et al. 2010[69]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, 2x iStent + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • baseline: 24.2 ± 1.8; 23.6 ± 1.5, *P* = 0.18 • 1 d: 21.9 ± 10.1; 26.4 ± 8.1, *P* = 0.08 • 1-2 wk: 16.5 ± 4.4; 18.2 ± 4.2, *P* = 0.28 • 1 mo: 16.7 ± 3.1; 18.9 ± 1.4, *P* = 0.01 • 3 mo: 15.2 ± 2.5; 18.6 ± 3.4, *P* = 0.009 • 6 mo: 15.6 ± 3.3; 19.6 ± 4, *P* = 0.02 • 12 mo: 17.6 ± 2.8; 19.8 ± 2.3, *P* = 0.04	• IOP was significantly lower in the 2x iStent + Phaco group vs. the Phaco alone group at every follow-up time point (except 1 d and 1-2 wk); no within-group statistical comparisons with baseline were conducted • The mean number of medications was not	*"With respect to efficacy, [2x iStent + Phaco] provided significant IOP reductions as well as a significant reduction in the need for concomitant medical treatment,"* p. 3331.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	Medications (number), mean ± SD (range), 2x iStent + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • baseline: 1.1 ± 0.5 (0-1); 1.2 ± 0.7 (0-2), *P* = 0.66 • 1 d: NR • 1-2 wk: NR • 1 mo: 0.1 ± 0.2 (0 to 1); 0.1 ± 0.3 (0 to 1), *P* = 0.51 • 3 mo: 0.1 ± 0.2 (0 to 1); 0.3 ± 0.5 (0 to 1), *P* = 0.06 • 6 mo: 0.1 ± 0.5 (0 to 2); 0.5 ± 0.7 (0 to 2), *P* = 0.03 • 12 mo: 0.00 (0); 0.7 ± 1.0 (0 to 3), *P* = 0.007 **Safety** **Intraoperative complications**, n (%), 2x iStent + Phaco and Phaco alone, respectively: • malpositioned stent: 6 (18% of the total number of stents implanted; number of eyes affected NR); NA	significantly different between groups at 1 d, 1-2 wk, 1 mo, or 3 mo follow-up, but was significantly lower in the 2x iStent + Phaco group vs. the Phaco alone group at 6 and 12 mo follow-up; no statistical comparisons with baseline were conducted • iStent malposition was present in 18% of the 2x iStent + Phaco group; no other intraoperative complications were reported	
Hydrus Microstent + Phaco Vs. Phaco Alone			
Samuelson et al. 2018[88]	**Clinical effectiveness** **Washed-out modified DIOP** (mm Hg), mean ± SD, Hydrus + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • baseline: 25.5 ± 3.0; 25.4 ± 2.9, *P* = NS • 24 mo: 17.4 ± 3.7; 19.2 ± 3.8, *P* = NR **Medicated IOP** (mm Hg), mean ± SD, Hydrus + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • baseline: 17.9 ± 3.1; 18.1 ± 3.1, *P* = NS • 24 mo: 16.8 ± 3.2; 17.4 ± 3.0, *P* = NR **Reduction in modified DIOP from baseline** (mm Hg), mean ± SD, Hydrus + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • 12 mo: –8.5; –6.3, between-group difference –2.2, *P* < 0.001 • 24 mo: –7.6 ± 4.1; –5.3 ± 4.2; between-group difference –2.3, 95% CI, –3.0 to –1.6 *P* < 0.001 **Proportion of eyes with washed-out modified DIOP reduction ≥ 20%,** %, Hydrus + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • 12 mo: 85.9%; 70.0%; between-group difference 15.9%, 95% CI, 11.2% to 27.8% *P* < 0.001	• The reduction in washed-out modified DIOP from baseline was significantly greater in the Hydrus Microstent + Phaco group vs. the Phaco alone group at 12 and 24 mo follow-up • A significantly greater proportion of eyes in the Hydrus Microstent + Phaco group vs. the Phaco alone group had ≥ 20%, 30%, or 40% reductions in washed-out modified DIOP at 24 mo • The reduction in	*"This 24-month multicenter randomized controlled trial demonstrated superior reduction in [modified DIOP] and medication use among subjects with mild-to-moderate POAG who received a [Hydrus Microstent] combined with phacoemulsification compared with phacoemulsification alone,"* p. 1. The reduction in unmedicated modified DIOP in *Hydrus Microstent + Phaco* vs. *Phaco alone* was *"stastistically and clinically significant,"* p. 6. *"There were no serious ocular*

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 24 mo: 77.3%; 57.8%; between-group difference 19.5%, *P* < 0.001 **Proportion of eyes with washed-out modified DIOP reduction ≥ 30%,** %, Hydrus + Phaco and Phaco alone, respectively (*P* value for between-group comparison): • 24 mo: 53.4%; 32.1%, *P* < 0.0001 **Proportion of eyes with washed-out modified DIOP reduction ≥ 40%,** %, Hydrus + Phaco and Phaco alone, respectively (*P* value for between-group comparison): • 24 mo: 24.7%; 8.0%, *P* < 0.0001 **Medications** (number), mean ± SD, Hydrus + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • baseline: 1.7 ± 0.9; 1.7 ± 0.9, *P* = NS • 24 mo: 0.3 ± 0.8; 0.7 ± 0.9, *P* = NR **Reduction in medications from baseline** (number), mean (%), Hydrus + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • 24 mo: 1.4 (82.4%); 1.0 (58.8%), between-group difference –0.4 medications, *P* < 0.001 **Safety** **Intraoperative adverse events,** n (%), Hydrus + Phaco and Phaco alone, respectively: • device malposition, 6 (1.6%); NA ○ device malposition within the iris root, 1 (0.3%); NA • hyphema obscuring the surgeon's view (resolved in < 1 wk), 4 (1.1%), 0.0% **Post-operative events,** n (%), Hydrus + Phaco and Phaco alone, respectively: • surgical re-intervention in study eye, 2.4%, 4.8% • uveitis/iritis requiring steroids, 5.6%, 3.7% • conjunctivitis, 5.7%, 7.0% • layered hyphema, > 2 mm after 1 day, 0.5%, 0.5% • BCVA loss ≥ 2 lines ≥ 3 mo, 1.4%, 1.6% • corneal abrasion, 1.1%, 0 • corneal edema, 1.4%, 0% • elevated IOP ≥ 10 mm Hg over baseline, 0.5%, 2.7% • device obstruction/focal PAS, nonobstructive, 14.9%, 2.1% • device obstruction/focal PAS, obstructive, 3.8%, NA	number of medications from baseline to 24 mo follow-up was significantly greater in the Hydrus Microstent + Phaco group vs. the Phaco alone group • There were relatively few intraoperative adverse events in the Hydrus Microstent + Phaco group (up to 1.6%) and none in the Phaco alone group (however those with complicated Phaco were excluded) • Adverse events, and requirement for secondary surgery, were similar between groups up to 24 mo follow-up, but this was not tested statistically	*adverse events related to the [Hydrus] microstent, and no significant differences in safety parameters between the 2 groups,"* p. 1.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• cystoid macular edema, 2.2%, 2.1% • epiretinal membrane, 1.6%, 1.6% • subconjunctival hemorrhage, 2.4%, 0% • worsening of VF mean deviation by 2.5 dB, 4.3%, 5.3% • development of neovascular glaucoma and secondary angle closure, 0%, 0.5% **Secondary IOP-lowering surgical interventions**, %, Hydrus + Phaco and Phaco alone, respectively: • tube shunts/Trabeculectomy, 0%, 2.1% • paracentesis, 0.3%, 1.0% • laser membranectomy/synechialysis, 0.8%, 0% • SLT/trabeculoplasty, 0%, 0.5% • **Total:** 1.1%, 2.7%		
Pfeiffer et al. 2015[71]	**Clinical effectiveness** **Proportion of patients with ≥ 20% reduction in washed-out DIOP compared with baseline, n (%)** (*P* values for between-group comparisons): • 12 mo: Hydrus + Phaco, NR (88%); Phaco, NR (74%); 95% CI, 16.3 to 51.7%; *P* = 0.1247 • 24 mo: Hydrus + Phaco, 40 (80%); Phaco, 23 (46%); 95% CI, 16.3 to 51.7%; *P* = 0.0008 **Washed-out DIOP**, mean ± SD, Hydrus + Phaco and Phaco, respectively (*P* values for between-group comparisons): • baseline: 26.3 ± 4.4; 26.6 ± 4.2, *P* = 0.7147 • 12 mo: 16.6 ± 2.8; 17.4 ± 3.7 • 24 mo: 16.9 ± 3.3; 19.2 ± 4.7, *P* = 0.0093 ○ washed-out DIOP was "*significantly lower than baseline*" (p. 1286) in both groups at both 12 and 24 months (*P* values NR) **Medications** (number), mean ± SD, Hydrus + Phaco and Phaco, respectively (*P* values for between-group comparisons): • baseline: 2.0 ± 1.0; 2.0 ± 1.1, *P* = 0.7619 • 24 mo: 0.5 ± 1.0; 1.0 ± 1.0, *P* = 0.0189 Note: Other values were reported only in figures (i.e., no data to report). **Safety** **Adverse events in year 1,** n (%),Hydrus + Phaco and Phaco, respectively: • retinal detachment: 0 (0.0%); 1 (2.0%), *P* = 1.0000	• DIOP was reduced from baseline in both groups, but was significantly lower in the Hydrus + Phaco group vs. the Phaco alone group at 24 mo follow-up • The number of medications was significantly lower in the Hydrus + Phaco group vs. the Phaco alone group at 24 mo follow-up • The proportion of patients with ≥ 20% reduction in washed-out DIOP compared with baseline was significantly greater in the Hydrus + Phaco group vs. the Phaco alone group at 24 mo follow-up • Adverse events were	*"Intraocular pressure was clinically and statistically significantly lower at 2 years in the* [Hydrus + Phaco] *group compared with the* [Phaco] *alone group, with no differences in safety,"* p. 1283.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• post-operative wound dehiscence: 0 (0.0%); 1 (2.0%), *P* = 1.000 • anterior ischemic optic neuropathy: 0 (0.0%); 1 (2.0%), *P* = 1.000 • BCVA loss > 2 lines: 0 (0.0%); 3 (6.0%), *P* = 0.2424 • IOP spike (> 10 mm Hg more than baseline): 2 (4.0%); 2 (4.0%), *P* = 1.0000 • macular edema: 1 (2.0%); 2 (4.0%), *P* = 1.0000 • retinal detachment: 0 (0.0%); 1 (2.0%), *P* = 1.0000 • vitreal macular traction: 0 (0.0%); 1 (2.0%), *P* = 1.0000 • epiretinal membrane: 0 (0.0%); 2 (4.0%), *P* = 0.4949 • focal peripheral anterior synechiae: 6 (12.0%); 1 (2.0%), *P* = 0.1117 • optic disc hemorrhage: 1 (2.0%); 0 (0.0%), *P* = 1.000 • secondary glaucoma surgery: 0 (0.0%); 0 (0.0%), *P* = NA **Adverse events in year 2,** n (%), Hydrus + Phaco and Phaco, respectively: • retinal detachment: 0 (0.0%); 0 (0.0%), *P* = NA • post-operative wound dehiscence: 0 (0.0%); 0 (0.0%), *P* = NA • anterior ischemic optic neuropathy: 0 (0.0%); 0 (0.0%), *P* = NA • BCVA loss > 2 lines: 0 (0.0%); 1 (2.0%), *P* = 1.000 • IOP spike (> 10 mm Hg more than baseline): 0 (0.0%); 0 (0.0%), *P* = NA • macular edema: 0 (0.0%); 0 (0.0%), *P* = NA • retinal detachment: 0 (0.0%); 0 (0.0%), *P* = NA • vitreal macular traction: 1 (2.1%); 0 (0.0%), *P* = 0.4948 • epiretinal membrane: 0 (0.0%); 1 (2.0%), *P* = 1.0000 • focal peripheral anterior synechiae: 9 (18.8%); 1 (2.0%), *P* = 0.0077 • optic disc hemorrhage: 0 (0.0%); 0 (0.0%), *P* = NA • secondary glaucoma surgery: 1 (2.1%); 2 (4.1%), *P* =1.0000	similar between groups at 1 y and 2 y follow-up, except for focal peripheral anterior synechiae, which was significantly more prevalent in the Hydrus + Phaco group at 2 y	
Other Comparisons (From Single Studies)			
Vold et al. 2016[70]	**Clinical effectiveness** **Unmedicated IOP** (mm Hg), mean ± SD, CyPass Micro-Stent + Phaco and Phaco alone, respectively (*P* values for between-group comparisons): • baseline: 24.4 ± 2.8; 24.5 ± 3.0, *P* > 0.05 • 24 mo: 17.0 ± 3.4; 19.3 ± 3.3, *P* = NR **Unmedicated IOP reduction from baseline** (mm Hg, %), mean ± SD, CyPass Micro-Stent + Phaco and Phaco alone, respectively (*P* values for comparisons between groups and within groups from baseline all *P* < 0.001): • 12 mo: –7.9 ± 4.1 (32%); –6.2 ± 3.8 (26%)	• The reduction in IOP and number of medications from baseline was greater in the CyPass Micro-Stent + Phaco vs. Phaco alone group at 12 and 24 mo follow-up • There were significantly fewer medications required in the CyPass	*"The [CyPass Micro-Stent] showed sustained 24-month efficacy benefit over phacoemulsification across several outcomes, including reducing both IOP and glaucoma medication use,"* p. 2108. *"Supraciliary implantation of*

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 24 mo: –7.4 ± 4.4 (30%); –5.4 ± 3.9 (21%) **Between-group difference in IOP** (mm Hg), mean (favouring CyPass Micro-Stent + Phaco): • 12 mo, PP: 1.7, 95% CI, 0.9 to 2.5, *P* < 0.001 • 24 mo, PP: 2.0, 95% CI, 1.1 to 2.8, *P* < 0.001 • 24 mo, ITT: 1.8, 95% CI, 1.0 to 2.6, *P* < 0.001 **IOP reduction ≥ 20% from baseline** (proportion of eyes), CyPass Micro-Stent + Phaco and Phaco alone, respectively (*P* values for between-group comparisons; variability presented in a figure, therefore no values to report): • 12 mo: 82%; 66%, *P* < 0.0001 • 24 mo, PP: 77%; 60%, *P* = 0.001 • 24 mo, ITT: 73%; 58%, *P* = 0.002 **Medications** (number), mean ± SD, CyPass Micro-Stent + Phaco and Phaco alone, respectively (*P* values for comparison with baseline unless otherwise stated): • baseline, ITT: 1.4 ± 0.9; 1.3 ± 1.0 (between group *P* > 0.05) • 12 mo, ITT: 0.2 ± 0.6 (*P* < 0.001); 0.7 ± 0.9 (*P* < 0.001) • 24 mo, ITT: "maintained" (values NR); 0.6 ± 0.8 (*P* < 0.001; between-group comparison, *P* < 0.001) Proportion of patients requiring **no medications** at 24 mo: • CyPass Micro-Stent + Phaco, 84.8%; Phaco alone, 59.1%, *P* < 0.001 ○ mean medication use at 24 mo was 67% lower in the CyPass Micro-Stent + Phaco group **Safety** **Adverse events** at any point intraoperatively or through 24 mo follow-up unless otherwise stated, n (%), CyPass Micro-Stent + Phaco; Phaco alone: • BCVA loss ≥ 10 letters (≥ 2 lines) of ≤ 30-day duration: 33 (8.8%); 20 (15.3%), *P* = 0.0466 • BCVA loss ≥ 10 letters (≥ 2 lines) unresolved at 24 mo: 1.1%; 0.0%, *P* = NR • corneal abrasion: 7 (1.9%); 2 (1.5%), *P* = 0.999 • corneal edema: 13 (3.5%); 2 (1.5%), *P* = 0.3741 • conjunctivitis: 4 (1.0%); 3 (2.3%), *P* = 0.3828 • cyclodialysis cleft ≥ 2-mm circumference: 7 (1.9%); 0 (0.0%), *P* = 0.1985 • hyphema, transient intraoperative: 10 (2.7%); 0 (0.0%), *P* = 0.0706 • iritis: 32 (8.6%); 5 (3.8%), *P* = 0.0809	Micro-Stent + Phaco vs. Phaco alone group at 12 and 24 mo follow-up • Adverse events were not different between groups	*the CyPass Micro-Stent during routine cataract surgery safely and sustainedly reduces IOP and glaucoma medication use in subjects with mild-to-moderate POAG and comorbid cataracts,"* p. 2110.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• hypotony (IOP < 6 mm Hg): 11 (2.9%); 0 (0%), *P* = 0.0744 • IOP ≥ 10 mm Hg over baseline: 16 (4.3%); 3 (2.3%), *P* = 0.4263 • maculopathy, cystoid edema: 6 (1.3%); 1 (0.8%), *P* = 0.6829 • tent obstruction: 8 (2.1%); NA, *P* = NA • subconjunctival hemorrhage: 6 (1.6%); 1 (0.8%), *P* = 0.6829 • secondary ocular surgical intervention: 20 (5.5%); 7 (5.3%), *P* = 0.9999 • visual field loss progression, confirmed: 25 (6.7%); 13 (9.9%), *P* = 0.2488 • **Total:** CyPass Micro-Stent + Phaco, 39%; Phaco alone, 36% Note: The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from this study that showed greater endothelial cell loss in the CyPass Micro-Stent group;[37,38] however, at the time of report publication, this device was still active in the MDALL and is therefore included in this report.		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery			
Goniotomy With Kahook Dual Blade + Phaco Vs. iStent + Phaco			
Dorairaj et al. 2018[86]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, KDB + Phaco and iStent + Phaco, respectively, *P* values for comparisons between groups or with baseline NR: • baseline: 17.9 ± 4.4; 16.7 ± 4.4 • 1 d: 15.4 ± 5.6; 16.0 ± 5.6 • 1 wk: 15.6 ± 5.5; 16.5 ± 5.5 • 1 mo: 14.0 ± 3.6; 14.9 ± 3.5 • 3 mo: 13.6 ± 2.7; 14.2 ± 2.6 • 6 mo: 13.6 ± 2.7; 13.9 ± 2.7 **IOP reduction from baseline** (mm Hg), mean (%), KDB + Phaco and iStent + Phaco, respectively (*P* values for comparison with baseline; all between-group comparisons *P* < 0.001): • 1 d: –2.5 (–13.9%), *P* < 0.001; –0.7 (–4.3%), *P* = 0.495 • 1 wk: –2.3 (–12.7%), *P* < 0.001; –0.2 (–0.9%), *P* = 0.999 • 1 mo: –3.8 (–21.3%), *P* < 0.001; –1.8 (–10.6%), *P* < 0.001 • 3 mo: –4.3 (–24.0%), *P* < 0.001; –2.5 (–15.0%), *P* < 0.001 • 6 mo: –4.2 (–23.7%), *P* < 0.001; –2.7 (–16.4%), *P* < 0.001 **Proportion of eyes with IOP reduction ≥ 20%** (%),KDB + Phaco and iStent + Phaco, respectively (*P* values for between-group comparisons): • 1 d: 40.9; 32.8, *P* = NS	• IOP was significantly reduced from baseline at 1, 3, and 6 mo in both groups; the reduction in IOP was significantly greater in the KDB + Phaco group vs. the iStent + Phaco group from 1 d through 6 mo follow-up • A significantly greater proportion of eyes achieved an IOP reduction of ≥ 20% in the KDB + Phaco group vs. the iStent + Phaco group at 1 wk through 6 mo follow-up • The number of medications was significantly lower, and	*"Goniotomy with the KDB combined with cataract surgery significantly lowers both IOP and the need for IOP-lowering medications compared to cataract extraction with iStent implantation in glaucomatous eyes through 6 months of postoperative follow-up,"* p. 791. *"Adverse events were generally mild to moderate in intensity and resolved spontaneously,"* p. 794.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 1 wk: 44.3; 24.2, *P* ≤ 0.011 • 1 mo: 53.6; 28.3, *P* ≤ 0.011 • 3 mo: 53.2; 26.8, *P* ≤ 0.011 • 6 mo: 56.1; 43.9, *P* ≤ 0.011 **Medications** (number), mean ± SD, KDB + Phaco and iStent + Phaco, respectively, *P* values for between-group differences: • baseline: 1.7 ± 0.9; 1.9 ± 0.9, *P* > 0.05 • 1 d: 0.9 ± 1.0; 0.9 ± -1.0, *P* > 0.05 • 1 wk: 1.1 ± 1.0; 1.0 ± 1.0, *P* > 0.05 • 1 mo: 0.6 ± 1.0; 1.0 ± 1.0, *P* < 0.05 • 3 mo: 0.6 ± 0.9; 1.0 ± 0.8, *P* < 0.05 • 6 mo: 0.6 ± 1.0; 1.0 ± 1.0, *P* < 0.05 **Medication reduction from baseline** (number), mean (%), KDB + Phaco and iStent + Phaco, respectively (*P* values for comparison with baseline unless otherwise specified): • 1 d: –0.8 (–47.1%), *P* < 0.001; –0.9 (–50.6%), *P* < 0.001; between-group comparison, *P* = 0.294 • 1 wk: –0.6 (–36.0%), *P* < 0.001; –0.9 (–47.0%), *P* < 0.001; between-group comparison, *P* = 0.078 • 1 mo: –1.1 (–64.6%), *P* < 0.001; –0.8 (–44.6%), *P* < 0.001; between-group comparison, *P* < 0.001 • 3 mo: –1.1 (–63.7%), *P* < 0.001; –0.9 (–48.8%), *P* < 0.001; between-group comparison, *P* = 0.001 • 6 mo: –1.1 (–62.9%), *P* < 0.001; –0.9 (–46.1%), *P* < 0.001; between-group comparison, *P* = 0.001 **BCVA** (logMAR), mean ± SD, value for both groups, *P* values for between-group differences: • baseline: 0.4 ± 0.3 • 6 mo: 0.1 ± 0.2, comparison with baseline *P* < 0.001 ○ "*No between-group differences in BCVA change were found (P = 0.999)"* p. 794 **Safety** **Adverse events**, n (%), KDB + Phaco and iStent + Phaco, respectively, *P* values for between-group differences: • corneal edema: 5 (2.1%); 3 (1.5%), *P* = 0.642	the reduction in medications from baseline significantly greater, in the KDB + Phaco group vs. the iStent + Phaco group at 1, 3, and 6 mo follow-up • BCVA improved significantly from baseline to 6 mo in both groups, and the change in BCVA was not significantly different between groups • Adverse events were not different between groups, with the exception of IOP spikes, which had a significantly greater incidence in the iStent + Phaco group; all adverse events resolved spontaneously	

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• inflammation: 1 (0.4%); 4 (2%); *P* = 0.116 • posterior capsule opacity: 1 (0.4%); 5 (2.5%), *P* = 0.060 • posterior vitreous detachment: 2 (0.8%); 2 (1%); *P* = 0.823 • rebound iritis: 2 (0.8%); 2 (1%), *P* = 0.823 • IOP spikes: 15 (6.3%); 25 (12.6%); *P* = 0.024 **Secondary surgical interventions:** NR		
Trabectome + Phaco Vs. 2x iStent + Phaco			
Kurji et al. 2017[79]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, Trabectome + Phaco and 2x iStent + Phaco, respectively (*P* values for between-group comparisons): • baseline: 20.92 ± 5.07; 17.47 ± 4.87, *P* = 0.026 • 6 mo: 16.0 ± 3.3; 13.6 ± 3.4, *P* = unclear (reported as *P* = 0.012 in the text but as *P* = NS in a figure) • 12 mo: shown only in a figure (i.e., no data to report), *P* > 0.05 **IOP reduction from baseline** (mm Hg), mean ± SD (%) (*P* values for between-group comparisons): • 6 mo: no difference between groups (reported as *P* = 0.430 in the text but as *P* < 0.05 in a figure); complete sample, –4.4 ± 4.8 • 12 mo: Trabectome + Phaco, –5.09 ± 5.73 (24%); 2x iStent + Phaco, –3.84 ± 3.80 (22%), *P* = 0.331; complete sample, –4.5 ± 4.9 **Medications** (number), mean ± SD (*P* values for between-group comparisons): • baseline: Trabectome + Phaco, 2.25 ± 1.34; 2x iStent + Phaco, 2.15 ± 1.21, *P* = 0.21 • 6 mo: no difference between groups (*P* = 0.387); complete sample, 1.6 ± 1.3 • 12 mo: no difference between groups (*P* = 0.947); complete sample, 1.8 ± 1.4 **Medication reduction from baseline** (number), mean ± SD, Trabectome + Phaco and 2x iStent + Phaco, respectively (*P* values for between-group comparisons): • 6 mo: –0.94 ± 1.24; –0.32 ± 0.59, *P* = 0.007 • 12 mo: –0.49 ± 1.17; –0.26 ± 0.73, *P* = 0.168 **BCVA change from baseline:** • 12 mo: Trabectome + Phaco, gained ~1.5 Snellen lines; 2x iStent + Phaco, gained ~2 Snellen lines, between-group comparison *P* = 0.417	• The reduction in IOP from baseline, and change in BCVA from baseline, were not different between groups at follow-up • The reduction in number of medications was greater in the Trabectome + Phaco group vs. the 2x iStent + Phaco group at 6 mo but not 12 mo follow-up • There were significantly more complications in the Trabectome + Phaco group vs. the 2x iStent + Phaco group	*"At 12 months of follow-up, both techniques significantly lowered IOP, but fewer complications were observed in the [2x iStent + Phaco] group,"* p. 99. "*[W]e conclude that, although both procedures are most relatively comparable in terms of efficacy, [2x iStent + Phaco] might be the safer option of these two MIGS procedures,"* p. 105.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	Safety **Overall complications, number of eyes (%):** • Trabectome + Phaco, reported as 32 (88.9%) in a table or 20 (55.6%) in the abstract; 2x iStent + Phaco, 5 (14.7%), *P* < 0.0001 **Post-operative complications:** • Trabectome + Phaco: Uveitis, n = 1; IOP spike, n = 1; blood clot, n = 1 • 2x iStent + Phaco: IOP spike, n = 2 **Early complications:** • Trabectome + Phaco: Uveitis, n = 9; hyphema, n = 5; IOP spike, n = 1; CME, n = 5; PAS, n = 5; AGSx, n = 1 • 2x iStent + Phaco: None • **Total early complications:** Trabectome + Phaco, n = 22 (62.9%); 2x iStent + Phaco, n = 0 (0%), *P* < 0.0001 **Late complications:** • Trabectome + Phaco: CME, n = 3; CRVO, n = 1; macular hole, n = 1; AGSx, n = 2 • 2x iStent + Phaco: Blocked iStent, n = 1 ○ between-group comparison, *P* = 0.09		
Khan et al. 2015[78]	**Clinical effectiveness** **IOP**[a] (mm Hg), mean ± SD, 2x iStent + Phaco and Trabectome + Phaco respectively (*P* values for between-group comparisons unless otherwise stated): • baseline: 19.6 ± 5.2 (SD reported as 5.3 in the abstract and text but as 5.2 in a table); 20.6 ± 6.8, *P* = 0.37 • 1 d: 14.5 ± 7.8; 16.8 ± 6.6, *P* = 0.08 • 1 wk: 17.2 ± 8.8; 19.7 ± 7.7, *P* = 0.035 • 1 mo: 14.9 ± 5.8; 15.8 ± 3.6, *P* = 0.57 • 3 mo: 14.4 ± 4.0; 15.5 ± 3.6, *P* = 0.39 • 6 mo: 13.8 ± 2.9; 16.5 ± 4.9, *P* = 0.041 • 12 mo: 14.3 ± 3.1 (compared with baseline *P* < 0.001); 17.3 ± 6.5 (compared with baseline *P* < 0.001), *P* = 0.011 **Medications**[a] (number), median [IQR], 2x iStent + Phaco and Trabectome + Phaco, respectively (*P* values for between-group comparisons unless otherwise stated): • baseline: 3.0 [2.0, 3.0]; 3.0 [2.0, 4.0], *P* = 0.53	• IOP was reduced from baseline in both groups, but was significantly lower in the 2x iStent + Phaco group vs. the Trabectome + Phaco group at 6 and 12 mo • The median number of medications was reduced from baseline in both groups, but was significantly lower in the 2x iStent + Phaco group vs. the Trabectome + Phaco group at 3, 6, and 12 mo • The incidence of	"[2x iStent] *and* [Trabectome] *combined with phacoemulsification led to a significant reduction in IOP and medication use, with the* [2x iStent + Phaco] *group achieving higher success and a lower rate of hypotony,"* p. 1723.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 1 d: 3.0 [2.0, 3.0]; 1.0 [0.0, 3.0], *P* < 0.001 • 1 wk: 2.0 [1.0, 3.0]; 3.0 [1.0, 3.0], *P* = 0.53 • 1 mo: 2.0 [1.0, 3.0]; 3.0 [2.0, 3.0], *P* = 0.05 • 3 mo: 2.0 [0.5, 3.0]; 3.0 [2.0, 4.0], *P* = 0.006 • 6 mo: 1.0 [0.0, 3.0]; 2.0 [2.0, 4.0], *P* = 0.012 • 12 mo: 1.0 [0.0, 2.0]; 2.0 [1.0, 3.0], *P* = 0.001; within-group comparisons with baseline both *P* < 0.001 **Medications** (number), mean ± SD, 2x iStent + Phaco and Trabectome + Phaco, respectively (*P* values NR): • baseline: 2.86 ± 0.91; 2.90 ± 1.10 • 1 d: 2.47 ± 1.10; 1.30 ± 1.53 • 1 wk: 2.22 ± 1.18; 2.40 ± 1.30 • 1 mo: 2.14 ± 1.30; 2.68 ± 1.24 • 3 mo: 1.77 ± 1.23; 2.54 ± 1.22 • 6 mo: 1.63 ± 1.40; 2.42 ± 1.36 • 12 mo: 1.22 ± 1.28; 2.15 ± 1.35 **Safety** **Adverse events**, n (%), 2x iStent + Phaco and Trabectome + Phaco, respectively: • hyphema: 2 (4%); 12 (23%), *P* = 0.008 • peripheral anterior synechiae formation: 10 (20%); 8 (15%), *P* = 0.61 • early post-operative interventions: 4 (8%); 2 (4%), *P* = 0.43 • intraocular pressure spike: 8 (16%); 17 (33%), *P* = 0.07 • transitory hypotony: 2 (4%); 0 (0%), *P* = 0.24 • glaucoma reoperation: 0 (0%); 4 (8%), *P* = 0.12 ○ Trabeculectomy (n = 3, at 6 d, 3.5 mo, and 9 mo), Trabectome revision and first stage GDD (n = 1, at 11 mo) • suprachoroidal hemorrhage: 0 (0%); 0 (0%), *P* = NA Note: For patients with reoperation (n = 4 in Trabectome + Phaco group), the values for IOP and number of medications prior to reoperation were used for the rest of the follow-up period (i.e., last observation carried forward).	hyphema was lower in the 2x iStent + Phaco group vs. the Trabectome + Phaco group, but there were no other significant between-group differences in adverse events	

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
Trabectome + MICS Vs. iStent/iStent Inject + MICS			
Gonnermann et al. 2017[77]	**Clinical effectiveness** **IOP reduction from baseline** at 12 mo post-operative (*P* values for comparison with baseline): • Trabectome + MICS: 30% (*P* < 0.001) • 2x iStent inject + MICS: 34% (*P* < 0.001) • no significant difference between groups at any time point (*P* > 0.05) • numerical values not reported for other follow-up time points **Number of glaucoma medications**, mean ± SD, Trabectome + MICS and 2x iStent inject + MICS, respectively (*P* values for comparison with baseline where applicable): • baseline: 2.08 ± 1.12; 2.04 ± 0.89 • 12 mo: 1.44 ± 1.29 (*P* < 0.05); 1.28 ± 1.17 (*P* < 0.05) • number of topical medications was significantly higher in Trabectome + MICS vs. 2x iStent inject + MICS at 6 wk post-operative due to post-operative treatment plan (*P* < 0.05), but there were no significant differences between groups at any other time point (all *P* > 0.05) **BCVA** (logMar), mean ± SD, Trabectome + MICS and 2x iStent inject + MICS, respectively (*P* values for comparison with baseline where applicable): • baseline: 0.38 ± 0.17; 0.32 ± 0.20 • 12 mo: 0.10 ± 0.12 (*P* < 0.001); 0.06 ± 0.09 (*P* < 0.001) • no significant difference between groups at any time point (*P* > 0.05) **Safety** Severe **intraoperative** and **post-operative complications**: None **Minor events**: • reflux bleeding occurred in 100% of patients and resolved spontaneously • Trabeculectomy had to be performed in 2/27 eyes in each group due to insufficient IOP lowering after MIGS	• Reduction in IOP and number of medications, improvement in BCVA, and safety, were similar between the Trabectome + MICS and 2x iStent Inject + MICS groups	*"Ab interno trabeculectomy [with Trabectome] and iStent® inject were both effective in lowering IOP with a favourable and comparable safety profile in an intraindividual comparative study over a 12-months follow-up in OAG. However, longer follow-up of these patients will be necessary to determine long-term outcomes and to evaluate significant differences,"* p. 359.
Different Numbers of iStents + Phaco			
Vlasov and Kim 2017[80]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, iStent + Phaco and 2x iStent + Phaco, respectively (*P* values for comparison with baseline unless otherwise stated): • baseline, different values reported in two separate tables: ○ study Table 1: 16.67 ± 4.1; 18.33 ± 3.99, between-group *P* = 0.0870 ○ study Table 2:16.67 ± 3.82; 18.33 ± 3.99, between-group *P* = 0.4996	• IOP was significantly reduced from baseline at 1, 3, 6, and 12 mo follow-up, but IOP was not different between groups at any time point	*"Both [iStent + Phaco* and *2x iStents + Phaco] demonstrated a significant reduction in IOP at 12 months. […] Only [2x iStent + Phaco] demonstrated a statistically significant reduction*

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 1 d: 20.17 ± 7.44 (*P* = 0.0128); 19.5 ± 8.22 (*P* = 0.4944), between-group *P* = 0.7348 • 1 wk: 16.78 ± 5.23 (*P* = 0.917); 15.83 ± 4.91 (*P* = 0.0376), between-group *P* = 0.4673 • 1 mo: 14.76 ± 3.77 (*P* = 0.0389); 13.85 ± 3.21 (*P* = 0.0001), between-group *P* = 0.3320 • 3 mo: 14.74 ± 4.77 (*P* = 0.0755); 14.17 ± 2.81 (*P* = 0.0001), between-group *P* = 0.6190 • 6 mo: 14.44 ± 4.27 (*P* = 0.0233); 14.71 ± 2.11 (*P* = 0.0014), between-group *P* = 0.8107 • 12 mo, different values for SDs reported in two separate tables: ○ study Table 1: 14.45 ± 3.8 (*P* = 0.0251); 14.31 ± 1.72 (*P* = 0.0014), between-group *P* = 0.9051 ○ study Table 2: 14.45 ± 3.96 (*P* = 0.0251); 14.31 ± 1.80 (*P* = 0.0014), between-group *P* = 0.9051 **IOP reduction from baseline** (%) at 12 mo post-operative, iStent + Phaco and 2x iStent + Phaco, respectively (P values for between-group comparison): • 13.3%; 21.9%; *P* = 0.9051 **Medications** (number), mean ± SD, iStent + Phaco and 2x iStent + Phaco, respectively (*P* values for comparison with baseline unless otherwise stated): • baseline: 2.33 ± 1.40; 2.37 ± 1.30, between-group *P* = 0.9205 • 1 d: 0.91 ± 1.44 (*P* = 0.0001); 1.2 ± 1.42 (*P* = 0.004), between-group *P* = 0.4298 • 1 wk: 1.29 ± 1.34 (*P* = 0.002); 0.93 ± 1.21 (*P* = 0.0001), between-group *P* = 0.2725 • 1 mo: 1.74 ± 2.58 (*P* = 0.2237); 1.12 ± 1.15 (*P* = 0.0005), between-group *P* = 0.2595 • 3 mo: 1.59 ± 2.48 (*P* = 0.1324); 1.3 ± 1.37 (*P* = 0.0067), between-group *P* = 0.6289 • 6 mo: 1.91 ± 2.35 (*P* = 0.3528); 1.71 ± 1.22 (*P* = 0.1020), between-group *P* = 0.7453 • 12 mo: 1.74 ± 2.47 (*P* = 0.2259); 1.15 ± 1.09 (*P* = 0.0066), between-group *P* = 0.4305 **Safety** **Intraoperative complications:** None **Complications**, iStent + Phaco group, n: • CME, 4 • increased IOP because of a steroid response, 2 • central retinal vein occlusion leading to development of anterior-chamber angle neovascularization and neovascular glaucoma, 1 **Complications**, 2x iStent + Phaco group: None	• At 12 mo, the number of medications was reduced from baseline only in the 2x iStent + Phaco group, and the number of medications was not significantly different between groups at any time point • There were no intraoperative complications in either group • There tended to be more post-operative complications in the iStent + Phaco group, but this was not tested statistically	*in medication burden,"* p. 222. *"No serious, vision-threatening complications were seen in our study that was directly attributable to the iStent,"* p. 225.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
Belovay et al. 2012[83]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD where reported, 2x iStent + Phaco and 3x iStent + Phaco, respectively (*P* values for between-group comparisons unless otherwise stated): • baseline: 17.3 ± 4.0; 18.6 ± 4.0, *P* = 0.24 • 1 mo: 13.4; 15.1, *P* = NS • 3 mo: 13.3; 14.5, *P* = NS • 6 mo: 13.5; 14.6, *P* = NS • 9 mo: data not reported • 12 mo: 13.8 (comparison with baseline, *P* < 0.001); 14.8 (comparison with baseline, *P* < 0.001), *P* = 0.78 **Reduction in IOP from baseline at 12 mo** (mm Hg), mean ± SD where reported, 2x iStent + Phaco and 3x iStent + Phaco, respectively: • –3.5; –3.9 ± 13.1, between-group comparison *P* = 0.76 **Proportion of patients with IOP ≤15 mm Hg at 12 mo,** n (%), 2x iStent + Phaco and 3x iStent + Phaco, respectively: • 21 (75%)*;* NR, between-group comparison *P* = NR **Medications** (n), mean ± SD, 2x iStent + Phaco and 3x iStent + Phaco, respectively, (*P* values for between-group comparisons unless otherwise stated): • baseline: 2.8 ± 0.8; 2.6 ± 1.2, *P* = 0.70 • 1 mo: 1.7; 1.0, *P* = NS • 3 mo: 1.2; 0.8, *P* = NS • 6 mo: 1.2; 0.4, *P* = 0.009 • 12 mo: 1.0 (comparison with baseline, P < 0.001); 0.4 (comparison with baseline, P < 0.001), *P* = 0.04 **No medications**, n (%), 2x iStent + Phaco and 3x iStent + Phaco, respectively: • 12 mo: 13 (46%); 18 (72%), *P* = NR **CDVA at 12 mo,** n (%), 2x iStent + Phaco and 3x iStent + Phaco, respectively, *P* values not reported: • 20/40 or better: 18 (64%); 19 (76%) • 20/50–20/100: 6 (21%); 5 (20%) • 20/200 or worse: 3 (11%); 1 (4%)	• IOP was significantly reduced from baseline at 12 mo follow-up in both groups, but was not significantly different between groups at any time point • The number of medications was significantly reduced from baseline at 12 mo in both groups (comparison with baseline NR at other time points), and was significantly lower in the 3x iStent + Phaco group vs. the 2x iStent + Phaco group at 6 and 12 mo follow-up • CDVA was similar between groups at 12 months but this was not tested statistically • Complications were not reported separately for each group	*"The implantation of 2 or 3 trabecular micro-bypass stents combined with cataract surgery was performed safely with a reduction in IOP and topical ocular hypotensive medications,"* p. 1916. *"Implantation of multiple trabecular micro-bypass stents has the potential to further reduce IOP and topical ocular hypotensive medications versus implantation of 1 trabecular micro-bypass stent,"* p. 1916.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	Safety **Overall complications**, n, *P* values NR: • blockage of the opening of the stent lumen, 8 eyes ○ these patients were treated with neodymium: YAG laser or argon laser (i.e., secondary interventions) • small hyphema, 1 eye • iStent not seated well, 1 eye • steroid response resulting in elevated IOP, 2 eyes • death due to unrelated systemic illness, 1 patient		
ECP + iStent + Phaco Vs. iStent + Phaco			
Ferguson et al. 2017[81]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD where reported, ECP + iStent + Phaco and iStent + Phaco, respectively (*P* values for comparison with baseline, where reported): • baseline: 21.49 ± 9.59; 20.66 ± 3.23 • 1 d: 15.78; 21.56 • 1 wk: 15.75; 18.46 • 1 mo: 15.31; 16.42 • 3 mo: 15.21; 16.36 • 6 mo: reported as 14.34 in a figure and 14.45 in the text (from the figure, 14.34 looks to be the correct value; $P < 0.01$); 16.00 • 12 mo: 14.35 ± 3.5 ($P < 0.01$); 16.18 ± 4.14 ($P < 0.01$) **Reduction in IOP** from baseline: • The IOP reduction was greater in ECP + iStent + Phaco (7.14 mm Hg) vs. iStent + Phaco (4.48 mm Hg) at 12 mo ($P < 0.01$); *P* values not reported for other time points • Mean reduction in IOP (mm Hg) from baseline to 12 mo post-operative follow-up, stratified by preoperative IOP, ECP + iStent + Phaco and iStent + Phaco, respectively (*P* values NR): ○ ≤ 16 mm Hg: 2.40; no eyes ○ 17-19 mm Hg: 4.23; 2.48 ○ 20-22 mm Hg: 5.91; 3.82 ○ ≥ 23 mm Hg: 12.89; 9.45 **Number of medications**, mean ± SD where reported, ECP + iStent + Phaco and iStent + Phaco, respectively (*P* values for comparison with baseline, where reported): • baseline: 1.78 ± 0.99; 1.68 ± 0.84 • 1 d: 1.71; 0.70	• IOP reductions were greater, but medication use was also higher, in the ECP + iStent + Phaco group vs. the iStent + Phaco group • When stratified by preoperative IOP, mean IOP reductions tended to be greater in those with higher initial IOP (not tested statistically) • Safety was similar across treatment groups	*"...although the IOP reduction was more significant in the study group [ECP + iStent + Phaco], the medication use was higher in this group postoperatively at 12 months, which might account for the lower IOP,"* p. 381. "*Patients who had implantation of the microbypass stent [iStent] in combination with cataract surgery and ECP had significantly better IOP reduction than those who did not have ECP. The combination procedure was also effective in patients with severe OAG,"* p. 377.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 1 wk: 1.92; 1.02 • 1 mo: 1.55; 0.74 • 3 mo: 1.62; 0.61 • 6 mo: 1.38 (*P* < 0.01); 0.78 • 12 mo: 1.10 ± 1.00 (*P* < 0.01); 0.62 (*P* < 0.01); between-group comparison *P* < 0.01 **Reduction in number of medications** from baseline: • The reduction in number of medications was greater (63% vs. 38%), and the number of medications was significantly lower in iStent + Phaco vs. ECP + iStent + Phaco at 12 mo (*P* < 0.01) • At 12 mo, 17 patients (35.4%) in ECP + iStent + Phaco were taking 0 medications **Safety** **IOP** increase of ≥15 mm Hg: • ECP + iStent + Phaco*:* n = 4 eyes (8%); iStent + Phaco*: "results were similar"* p. 379 (values not reported) **Need for secondary surgery** (n), ECP + iStent + Phaco and iStent + Phaco, respectively: • 2 eyes; 2 eyes **Significant post-operative complications:** None		
ECP + Phaco Vs. Trabectome + Phaco			
Moghimi et al. 2018[89]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, ECP + Phaco and Trabectome + Phaco, respectively (*P* values for between-group comparisons): • baseline: 20.6 ± 5.4; 18.7 ± 4.7, *P* = 0.30 • 1 d: 21.5 ± 9.6; 13.6 ± 4.7, *P* = 0.003 • 1 wk: 15.3 ± 5.1; 15.5 ± 6.3, *P* = 0.99 • 1 mo: 18.0 ± 5.8; 15.3 ± 3.5, *P* = 0.15 • 3 mo: 16.5 ± 5.2; 14.1 ± 3.3, *P* = 0.18 • 6 mo: 16.0 ± 5.3; 13.9 ± 2.9, *P* = 0.17 • 12 mo: 16.7 ± 4.3; 15.4 ± 4.4, *P* = 0.45 **Medications** (number), mean ± SD, ECP + Phaco and Trabectome + Phaco, respectively (*P* values for between-group comparisons): • baseline: 2.0 ± 1.0; 1.3 ± 1.2, *P* = 0.06	• IOP was numerically reduced from baseline up to 12 mo follow-up in both groups, but this was not tested statistically • IOP was transiently greater in ECP + Phaco versus Trabectome + Phaco at 1 day post-operative, but there were no significant differences between groups at any other time point • The number of medications was not	*"All procedures significantly lowered IOP. [Trabectome + Phaco] resulted in fewest complications,"* p. 557.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 1 wk: 0.3 ± 0.7; 0.0 ± 0.0, *P* = 0.05 • 1 mo: 0.5 ± 0.9; 0.2 ± 0.6, *P* = 0.30 • 3 mo: 0.8 ± 1.0; 0.3 ± 0.7, *P* = 0.09 • 6 mo: 0.8 ± 1.1; 0.3 ± 0.5, *P* = 0.05 • 12 mo: 1.2 ± 1.1; 0.7 ± 0.9, *P* = 0.12 **Visual field** (dB), mean ± SD, ECP + Phaco and Trabectome + Phaco, respectively (*P* values NR): • baseline: –9.1 ± 5.7; –8.0 ± 4.3 • 12 mo: –8.0 ± 6.1; –6.5 ± 4.2 ○ *"After 1 year, there were no significant differences in the mean change in any group"* p. 560 **Safety** **Complications**, n (%), ECP + Phaco and Trabectome + Phaco, respectively: • fibrin reaction: 7 (20%); 0 (0%) • hyphema: 3 (9%); 6 (23%) • layered hyphema: 1 (3%); 1 (4%) • IOP spike (≥ 10 mm Hg increase from baseline): 7 (20%); 1 (4%) • no severe complications *"such as a shallow anterior chamber, bleb leak, choroidal detachment, hypotony, or infection"* ○ *P* values were only reported for comparisons across three groups (the third group did not meet eligibility criteria for inclusion in the present report) **Requirement for secondary glaucoma surgery:** None	significantly different between groups at baseline or any follow-up time point • The mean change in VF from baseline to 12 mo follow-up was not significantly different between groups • The number of complications was not compared statistically between groups • No patients (in either group) required secondary surgery	
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery			
Ting et al. 2018[87]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, Trabectome + Phaco and Trabeculectomy + Phaco, respectively (*P* values for between-group comparisons): • baseline: 20.0 ± 5.3; 23.1 ± 6.4, *P* = 0.22 • 6 mo: 17.5 ± 3.8; 16.0 ± 6.0, *P* = 0.54 • 12 mo: 16.8 ± 2.7; 17.1 ± 5.0, *P* = 0.57 **Reduction in IOP from baseline** (mm Hg), mean ± SD, Trabectome + Phaco and Trabeculectomy + Phaco, respectively (*P* values for between-group comparisons): • 6 mo: –2.8 ± 3.2; –7.4 ± 9.7, *P* = 0.54	• IOP, reduction in IOP from baseline, and number of medications were not significantly different between groups at any time point, but the study was likely underpowered • There were no significant between-group	*"[Trabectome + Phaco] achieved similar IOP lowering at 6 and 12 months compared with [Trabeculectomy + Phaco] with a similar number of glaucoma medications required at 1 year and no serious complications identified in the [Trabectome + Phaco] group. Our results with [Trabectome +

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 12 mo: –2.7 ± 5.3; –6.4 ± 8.7, *P* = 0.35 **Medications** (number), mean ± SD, Trabectome + Phaco and Trabeculectomy + Phaco, respectively (*P* values for between-group comparisons): • baseline: 1.80 ± 1.31; 1.40 ± 1.13, *P* = 0.59 • 6 mo: 0.78 ± 1.39; 0.38 ± 0.74, *P* = 0.68 • 12 mo: 0.44 ± 0.88; 0.75 ± 0.89, *P* = 0.41 **Safety** **Early post-operative complications** (≤ 30 days post-operative), n %, Trabectome + Phaco and Trabeculectomy + Phaco, respectively, between-group comparison *P* = 0.60: • **Mild:** ○ PAS: 5 (50%); 1 (11%) • **Moderate:** ○ day 1 IOP spike: 5 (50%); 3 (33%) ○ hyphema: 4 (40%); 0 (0%) ○ hypotony: 1 (10%); 3 (33%) ○ bleb leak: NA; 2 (22%) ○ steroid response: 1 (10%); 0 (0%) • **Severe:** ○ hypotony maculopathy: 0 (0%); 2 (22%) ○ choroidal effusion: 0 (0%); 2 (22%) **Late post-operative complications** (> 30 days post-operative), n %, Trabectome + Phaco and Trabeculectomy + Phaco, respectively, between-group comparison *P* = 0.41: • **Mild:** ○ PAS: 5 (50%); 2 (22%) • **Moderate:** ○ chronic/recurrent uveitis: 2 (22%); 2 (22%) ○ encapsulated bleb: NA; 1 (11%) • **Severe:** ○ hypotony maculopathy: 0 (0%); 0 (0%) ○ choroidal effusion: 0 (0%); 0 (0%) **Secondary glaucoma surgery,** n %, Trabectome + Phaco and Trabeculectomy + Phaco, respectively: 1 (10%); 0 (0%); *P* = 0.36	differences in early or late post-operative complications, or need for secondary glaucoma surgery, but the study was likely underpowered	*Phaco] are consistent with existing literature, supporting its favourable safety profile for patients with comorbid cataracts, mild to moderate glaucoma, and either a target IOP reduction to the mid- to high teens or decreased reliance on topical glaucoma medications. However, for patients with more advanced glaucoma requiring IOP reduction into the low to mid-teens, we suggest [Trabeculectomy + Phaco] should be considered, keeping in mind the increased risk of severe complications,"* p. 6. *"Mild and moderate complications were seen in both treatment groups, but severe complications were seen only in the [Trabeculectomy + Phaco group]. One secondary glaucoma procedure was required in the [Trabectome + Phaco] group,"* p. 1.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
Kinoshita-Nakano et al. 2018[85]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, Trabectome + Phaco and Trabeculotomy + Phaco, respectively (*P* values for between-group comparisons): • baseline: 21.0 ± 5.7; 23.0 ± 7.0, *P* = 0.33 • 3 mo: 14.5 ± 3.3; 14.3 ± 2.5, *P* = 0.97 • 6 mo: 15.1 ± 3.6; 15.0 ± 2.7, *P* = 0.77 • 12 mo: 15.6 ± 3.5; 15.3 ± 3.2, *P* = 0.53 • 18 mo: 15.4 ± 3.3; 14.9 ± 2.9, *P* = 0.58 • 24 mo: 14.9 ± 2.8; 15.0 ± 3.4, *P* = 0.70 • 36 mo: 14.6 ± 2.5; 14.6 ± 3.2, *P* = 0.48 **Reduction in IOP from baseline** (%), mean ± SD, Trabectome + Phaco and Trabeculotomy + Phaco, respectively (*P* values for between-group comparisons): • 3 mo: 27.7 ± 20.1; 34.3 ± 15.4, *P* = 0.15 • 6 mo: 25.9 ± 20.2; 32.0 ± 13.9, *P* = 0.19 • 12 mo: 21.8 ± 20.7; 30.3 ± 16.5, *P* = 0.050 • 18 mo: 20.5 ± 19.5; 33.0 ± 23.4, *P* = 0.042 • 24 mo: 22.0 ± 18.0; 33.4 ± 14.8, *P* = 0.025 • 36 mo: 26.5 ± 25.0; 33.9 ± 14.0, *P* = 0.074 **Medications** (number), mean ± SD, Trabectome + Phaco and Trabeculotomy + Phaco, respectively (*P* values for between-group comparisons): • baseline: 3.2 ± 0.9; 3.2 ± 0.8, *P* = 0.49 • 3 mo: 2.3 ± 1.3; 0.9 ± 0.6, *P* < 0.0001 • 6 mo: 2.1 ± 1.3; 1.3 ± 0.8, *P* = 0.004 • 12 mo: 2.2 ± 1.5; 1.6 ± 1.2, *P* = 0.027 • 18 mo: 2.6 ± 1.4; 2.3 ± 1.4, *P* = 0.055 • 24 mo: 2.7 ± 1.2; 2.5 ± 1.4, *P* = 0.078 • 36 mo: 2.7 ± 1.4; 2.5 ± 1.4, *P* = 0.67 **Safety** None reported exclusively for the subgroup of interest	• IOP was not different between groups at baseline or any follow-up time point • The % reduction in IOP from baseline was significantly greater in the Trabeculotomy + Phaco group vs. the Trabectome + Phaco group at 18 and 24 mo only • The number of medications was significantly lower in the Trabeculotomy + Phaco group vs. the Trabectome + Phaco group at 3, 6, and 12 mo follow-up but was not different between groups at 18, 24, or 36 mo	*"IOP reduction targets and expected success rates may not be very different between the two surgical procedures,"* p. 7.
Marco et al. 2017[82]	**Clinical effectiveness** **IOP** (mm Hg), mean ± SD, ECP + Phaco and Trab + Phaco, respectively (*P* values for between-group comparisons): • baseline: 19.9 ± 10.2; 19.2 ± 7.2, *P* = 0.589	• IOP was not different between groups at baseline or 6 mo follow-up; IOP was transiently	*"Overall, while [ECP + Phaco] produced similar improvements in IOP and visual acuity as [Trab + Phaco] at 6 months,*

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	• 1 d: 22.1 ± 7.8; 16.0 ± 12.3, *P* = 0.008 • 6 mo: 14.2 ± 3.6; 13.0 ± 2.5, *P* = 0.240 **Reduction in IOP from baseline** (mm Hg), mean ± SD: • 6 mo: ECP + Phaco, –5.7 ± 10.8; Trab + Phaco, –6.2 ± 7.4, *P* = 0.376 **Reduction in IOP from baseline** (%), mean ± SD: • 6 mo: ECP + Phaco, 28.8 ± 34.0; Trab + Phaco, 31.4 ± 25.5, *P* = 0.428 **Medications** (number), mean ± SD, ECP + Phaco and Trab + Phaco, respectively (*P* values for between-group comparisons): • baseline: 2.5 ± 1.2; 2.7 ± 1.2, *P* = 0.667 • 6 mo: 1.39 ± 1.09; 0.48 ± 0.92, *P* = 0.0064 • number of medications was significantly greater in ECP + Phaco vs. Trab + Phaco from week 1 to 6 mo (*P* < 0.005; data shown only in a figure, therefore no values to report) **Reduction in medications from baseline** (number), mean ± SD: • 6 mo: ECP + Phaco, 1.17 ± 1.13; Trab + Phaco, 2.10 ± 1.47, *P* = 0.023 **Change in VA from baseline** (logMAR), mean ± SD, ECP + Phaco and Trab + Phaco, respectively: • 1 wk: NR; "*significantly reduced*" (p. 180; *P* = 0.03 compared with baseline) • 6 mo: 0.24 ± 0.50 (from approximately 20/90 to 20/50); 0.33 ± 0.48 (from approximately 20/80 to 20/35), between-group comparison *P* = 0.388 **Safety** IOP spike, number (%): • 1 d: ECP + Phaco, 12 (50.0%); Trab + Phaco, 6 (20.7%), *P* = 0.040 **Intraoperative complications:** ECP + Phaco: • posterior capsular rupture with vitreous loss requiring anterior vitrectomy (n = 2), hyphema preventing application of further laser (n = 1) Trab + Phaco: • none	greater post-operative (at 1 d) in the ECP + Phaco group vs. the Trab + Phaco group, possibly due to retained viscoelastic (part of the ECP procedure) • The reduction in medication use from baseline was greater in the Trab + Phaco group vs. the ECP + Phaco group • VA was significantly improved at 6 mo in both groups • There tended to be more intraoperative complications in ECP + Phaco group vs. the Trab + Phaco group, and more early and late post-operative complications in the Trab + Phaco group, but these differences were not tested statistically	*[ECP + Phaco] was associated with fewer cases of complete success, with many patients requiring additional medications. In addition, patients in the [ECP + Phaco] group experienced higher immediate IOP spikes and anterior chamber inflammatory reactions. In comparison, [Trab + Phaco] patients experienced higher levels of complete success, without the need of postoperative medications,"* p. 182.

Study Citation	Quantitative Findings or Narrative Summary	Interpretation	Authors' Conclusions
	Early (< 30 d) post-operative complications: ECP + Phaco: • none Trab + Phaco: • hypotony (n = 5), serous choroidal effusion (n = 1), bleb leak (n = 1), laser suture lysis (n = 13), bandage contact lens (n = 3) **Late (> 30 d) post-operative complications:** ECP + Phaco: • none Trab + Phaco: • needling of bleb (n = 2)		

1x = one device; 2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; AGSx = additional glaucoma surgery; BCVA = best-corrected visual acuity; CDVA = corrected-distance visual acuity; CI = confidence interval; CME = cystoid macular edema; d = days; dB = decibel; DIOP = diurnal intraocular pressure; ECP = endoscopic cyclophotocoagulation; GDD = glaucoma drainage device; GDD-2 = second Baerveldt glaucoma implant 250 or 350; Hydrus = Hydrus Microstent; HR = hazard ratio; IOP = intraocular pressure; IQR = inter-quartile range; ITT = intention-to-treat; LASIK = laser in situ keratomileusis; logMAR = logarithm of the minimum angle of resolution; LP = light perception; LPI = laser peripheral iridotomy; MDALL = Medical Devices Active Licence Listing; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = month; NR = not reported; NS = non-significant; PAS = peripheral anterior synechiae; Phaco = phacoemulsification; PSD = pattern standard deviation; PP = per-protocol; QoL = quality of life; SLT = selective laser trabeculoplasty; Trab + Phaco = Trabeculectomy with mitomycin C + Phacoemulsification; VA = visual acuity; VF = visual field; vs. = versus; wk = week; y = year; YAG = yttrium-aluminum-garnet.

Appendix 13: GRADE Evidence Profile Tables — Clinical Review

Additional GRADE Tables for Research Question 1

Table 32: Effect of MIGS Versus Comparators on IOP in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS Vs. Pharmacotherapy: 2x iStent Vs. Travoprost, or 2x iStent Inject Vs. Latanoprost + Timolol											
2	RCT[a]	Very serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	None	2x iStent, 54 2x iStent Inject, 94	Travoprost, 47 Latanoprost + Timolol, 98	**MIGS [?] Pharmacotherapy: IOP** was numerically reduced from baseline at 1 to 36 mo following 2x iStent or Travoprost (reduction of ~10 mm Hg),[58] or at 1 to 12 mo following 2x iStent Inject or Latanoprost + Timolol (reduction of ~8 mm Hg),[36] but differences within or between groups were not tested statistically.[36,58]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Laser Therapy: Hydrus Microstent Vs. SLT											
1	Prospective cohort[d]	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	None	56	31	**MIGS = Laser Therapy: IOP** was significantly reduced from baseline at 1 to 12 mo following Hydrus Microstent or SLT (reduction of ~4 mm Hg to 7 mm Hg), but was not significantly different between groups at any time point.[62]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Another MIGS: 1x Vs. 2x Vs. 3x iStent											
1	RCT[g]	Serious risk of bias[g]	No serious inconsistency	No serious indirectness	Serious imprecision[i]	None	iStent, 38 2x iStent, 41	NA[j]	**1 iStent < 2 iStents < 3 iStents: IOP** was significantly reduced from baseline in all groups at 18 mo follow-up and the reduction was incrementally greater with increasing numbers of iStents (reduction of ~4 mm Hg, 6 mm Hg, and 8 mm Hg for 1, 2, and 3	⊕⊕OO LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
							3x iStent, 40		iStents, respectively; not tested statistically at other follow-up time points up to 42 mo).[59,60]		
MIGS Vs. Filtration Surgery: ECP Vs. Glaucoma Drainage Device											
2	Retrospective cohort and non-randomized controlled clinical trial[k]	Serious risk of bias[l]	No serious inconsistency	No serious indirectness	No serious imprecision	None	59	BGI, 48 AGI, 34	**MIGS = Glaucoma Drainage Device:** Retrospective cohort study: **IOP** was significantly reduced from baseline (reduction of ~7 mm Hg to 11 mm Hg) in both ECP and BGI groups at 3 to 24 mo follow-up, but was not different between groups at any time point.[63] Non-randomized controlled clinical trial: **IOP** was significantly reduced from baseline (reduction of ~19 mm Hg to 36 mm Hg) in both ECP and AGI groups from 1 wk to 24 mo follow-up (only tested statistically at 24 mo); the reduction in IOP was significantly greater in AGI vs. ECP at 1 wk, in ECP vs. AGI at 2, 3, and 4 mo, and was not significantly different between groups thereafter up to 24 mo follow-up.[61]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: Trabectome Vs. Trabeculectomy With MMC											
2	Prospective cohort and retrospective cohort[m]	Serious risk of bias[n]	No serious inconsistency[o]	No serious indirectness	Serious imprecision[p]	None	158	127	**Mixed Findings; Trabectome [?]/< Trabeculectomy With MMC:** Prospective cohort study: **IOP** was significantly reduced from baseline (reduction of ~4 mm Hg to 15 mm Hg) in both the Trabectome and Trabeculectomy groups at 6 mo (to ~14.7 mm Hg and 12.9 mm Hg, respectively), but between-group differences	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									were not tested statistically.[25] Retrospective cohort study: **IOP** was numerically reduced from baseline in both groups (not tested statistically), and was significantly higher in the Trabectome vs. Trabeculectomy group at all follow-up time points (1 to 30 mo; at 30 mo IOP ~16.6 and 10.0 mm Hg respectively).[64]		
MIGS Vs. Filtration Surgery: 2x iStent Inject Vs. Trabeculectomy With MMC											
1	Prospective cohort[q]	Serious risk of bias[r]	No serious inconsistency	No serious indirectness	Serious imprecision[s]	None	20	25	**2x iStent Inject [?] Trabeculectomy with MMC:** **IOP** was significantly reduced from baseline (reduction of ~5 mm Hg to 15 mm Hg) in both 2x iStent Inject and Trebculectomy groups at 6 mo (to ~16.0 mm Hg and 12.9 mm Hg, respectively), but between-group differences were not tested statistically.[25]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: Trabectome or 2x iStent Inject Vs. Trabeculectomy With MMC											
1	Prospective cohort[q]	Serious risk of bias[r]	No serious inconsistency	No serious indirectness	Serious imprecision[s]	None	63	25	**MIGS = Trabeculectomy with MMC:** **IOP** was significantly lower in the Trabeculectomy vs. MIGS (combined Trabectome and 2x iStent Inject) groups at 6 wk and 3 mo (by ~2 mm Hg to 3 mm Hg), but there was no significant difference between groups at 6 mo follow-up.[25]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: Xen45 With MMC Vs. Trabeculectomy With MMC											
1	Retrospective cohort[t]	Serious risk of bias[u]	No serious inconsistency	No serious indirectness	Serious imprecision[v]	None	185	169	**Xen45 with MMC = Trabeculectomy with MMC:** **IOP** was not significantly different between Xen45 and	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings			Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									Trabeculectomy groups at follow-up (median follow-up duration of 15.0 and 17.8 mo, respectively).[65]		

= = not significantly different between groups; > = intervention more favourable than comparator; < = intervention less favourable than comparator; [?] = not compared statistically or non-interpretable; 1x = one device; 2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; BGI = Baerveldt glaucoma implant; ECP = endoscopic cyclophotocoagulation; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = months; NA = not applicable; no. = number; RCT = randomized controlled trial; SLT = selective laser trabeculoplasty; vs. = versus; wk = weeks; y = years.

Note: Data were collected by RCT, non-randomized controlled clinical trial, retrospective or prospective cohort, with up to 42 months of follow-up. IOP was measured by Goldmann applanation tonometry.

[a] Two RCTs.[36,58]

[b] Very serious risk of bias. Selection bias: no indication of allocation concealment.[36,58] Detection bias: unclear whether diurnal variation accounted for in measurement of IOP;[58] no blinding of outcome assessors.[36,58] Attrition bias: low-risk at 12- and 24-month follow-up; large amount of missing data at 36-month follow-up and reasons not reported.[58] Reporting bias: no statistical comparisons conducted;[58] insufficient reporting of *P* values.[36]

[c] Serious imprecision. No measures of variability in one study,[58] and wide confidence intervals leading to uncertainty about the true magnitude of the effect in the other.[36]

[d] One prospective cohort study.[62]

[e] Serious risk of bias.[62] Bias due to confounding: significant differences between groups at baseline were not controlled, and treatment arm was assigned by geographical location. Bias in measurement of outcome: diurnal variation was not accounted for in measurement of IOP.

[f] Serious imprecision. Only a single study, and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).[62]

[g] One RCT in two publications.[59,60]

[h] Serious risk of bias.[59,60] Selection bias: no indication of allocation concealment. Detection bias: unclear whether diurnal variation accounted for in measurement of IOP.

[i] Serious imprecision. Only a single study.[59,60]

[j] In this study, eyes with different numbers of iStents (all MIGS) were compared.[59,60]

[k] One retrospective cohort[63] and one non-randomized controlled clinical trial.[61]

[l] Serious risk of bias.[61,63] Bias due to confounding: different surgeons performed endoscopic cyclophotocoagulation and BGI surgery;[63] pseudorandomization (first patient randomized, followed by counterbalanced enrolment);[61] potential confounding variables not controlled for in analyses.[61,63] Bias in selection of participants: only those with two-year complete data were included and it is possible that those with complete data were systematically different from those without complete data (i.e., different from those in routine clinical practice).[63] Bias due to missing data: large loss to follow-up, amount of missing data not balanced across groups, and reasons for missing data not reported.[61,63] Bias in measurement of outcomes: diurnal variation was not accounted for in measurement of IOP; IOP was measured without medication washout and the number of medications was significantly different between groups.[63] Bias in selection of the reported result: some preoperative population characteristics that were measured were not reported.[63]

[m] One prospective cohort[25] and one retrospective cohort study.[64]

[n] Serious risk of bias.[25,64] Bias due to confounding: decision for MIGS versus Trabeculectomy was made by treating surgeon based on patient characteristics, and choice of MIGS was made by individual patients;[25] retrospective study and rationale for assigning treatments likely to be different between groups;[64] significant differences between groups at baseline;[64] potential confounding variables not controlled for in analyses.[25,64] Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups).[25,64] Bias due to missing data: large loss to follow-up and reasons for missing data not reported.[64] Bias in measurement of outcomes: diurnal variation was not accounted for in measurement of IOP; IOP was measured without medication washout and the number of medications was significantly different between groups.[25,64]

[o] No serious inconsistency. Mixed findings may be due to between-study differences in patient characteristics,[25,64] lack of between-group statistical comparison in one study,[25] and/or differences in sample size (for the Trabectome and Trabeculectomy groups, respectively: 43 and 25 eyes[25] versus 115 and 102 eyes).[64]

[p] Serious imprecision. No measures of variability in one study.[25]

[q] One prospective cohort study.[25]

[r] Serious risk of bias.[25] Bias due to confounding: decision for MIGS versus Trabeculectomy was made by treating surgeon based on patient characteristics, and choice of MIGS was made by individual patients; potential confounding variables not controlled for in analyses. Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias in measurement of outcomes: diurnal variation was not accounted for in measurement of IOP; IOP was measured without medication washout and the number of medications was significantly different between groups.

[s] Serious imprecision. Only a single study, and no measures of variability.[25]

[t] One retrospective cohort study.[65]

[u] Serious risk of bias.[65] Bias due to confounding: significant differences between groups at baseline; potential confounding variables not controlled for in analyses. Bias in selection of participants: patients with < 1 month follow-up were excluded and it is possible that those with <1 month follow-up were systematically different from those with ≥ 1 month follow-up (i.e., different from those in routine clinical practice). Bias due to missing data: no information on amount or nature of missing data was reported. Bias in measurement of outcomes: diurnal variation was not accounted for in measurement of IOP. Bias in selection of the reported result: no rationale for reporting findings as medians instead of means, and absolute values reported only at “last follow-up.”

[v] Serious imprecision. Only a single study.[65]

Table 33: Effect of MIGS Versus Comparators on Proportion of Eyes Achieving IOP Targets

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS Vs. Pharmacotherapy: 2x iStent Vs. Travoprost, or 2x iStent Inject Vs. Latanoprost + Timolol											
2	RCT[a]	Very serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	None	2x iStent, 54 2x iStent Inject, 94	Travoprost, 47 Latanoprost + Timolol, 98	**Mixed Findings; MIGS [=]/>/[>] Pharmacotherapy:** **≥ 20%, 30%, or 40% IOP reduction** from baseline (12 follow-up): • 2x iStent Inject [=] Latanoprost + Timolol[36] **≥ 50% IOP reduction** from baseline (12 follow-up): • 2x iStent Inject > Latanoprost + Timolol[36] **IOP ≤ 18 mm Hg**: • 2x iStent [>] Travoprost (at 12, 24, and 36 mo follow-up)[58] • 2x iStent Inject [=] Latanoprost + Timolol groups (at 12 mo follow-up)[36] **IOP ≤ 15 mm Hg**: • 2x iStent [>] Travoprost (at 12, 24, and 36 mo follow-up)[58] • 2x iStent Inject [=] Latanoprost + Timolol groups (at 12 mo follow-up)[36]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Laser Therapy: Hydrus Microstent Vs. SLT											
1	Prospective cohort[d]	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	None	56	31	**MIGS [=] Laser Therapy:** **> 20% IOP reduction** from baseline (12 mo follow-up): • Hydrus Microstent [=] SLT[62]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Another MIGS: 1x Vs. 2x Vs. 3x iStent											
1	RCT[g]	Serious risk of bias[h]	No serious inconsistency	No serious indirectness	Serious imprecision[i]	None	iStent, 38 2x iStent,	NA[j]	**3 iStents [=] 2 iStents [=] 1 iStent:** **≥ 20% IOP reduction** from baseline (12 and 48 mo follow-up): • no between-group difference [59,60] **IOP ≤ 18 mm Hg** (12 mo follow-up):	⊕⊕OO LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
							41 3x iStent, 40		• no between-group difference[59,60] **IOP ≤ 15 mm Hg** (12 mo follow-up): • *3x* [>] *2x* [>] *1x* iStent[59,60]		
MIGS Vs. Filtration Surgery: ECP Vs. AGI											
1	Non-randomized controlled clinical trial[k]	Serious risk of bias[l]	No serious inconsistency	No serious indirectness	Serious imprecision[m]	None	34	34	**MIGS = Glaucoma Drainage Device:** **IOP > 6 mm Hg and < 21 mm Hg with/without medication** 12 and 24 mo follow-up: • ECP = AGI[61]	⊕OOO VERY LOW	CRITICAL

= = not significantly different between groups; [=] = not compared statistically but tendency for no difference between groups; > = intervention more favourable than comparator; [>] = not compared statistically but tendency for intervention more favourable than comparator; 1x = one device; 2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; ECP = endoscopic cyclophotocoagulation; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; mo = months; no. = number; RCT = randomized controlled trial; SLT = selective laser trabeculoplasty; vs. = versus.

Note: Data were collected by RCT, non-randomized controlled clinical trial, or prospective cohort, with up to 42 months of follow-up. IOP was measured by Goldmann applanation tonometry.

[a] Two RCTs.[36,58]

[b] Very serious risk of bias. Selection bias: no indication of allocation concealment.[36,58] Detection bias: unclear whether diurnal variation accounted for in measurement of IOP;[58] no blinding of outcome assessors.[36,58] Attrition bias: low-risk at 12- and 24-month follow-up; large amount of missing data at 36-month follow-up and reasons not reported.[58] Reporting bias: no statistical comparisons conducted;[58] insufficient reporting of *P* values.[36]

[c] Serious imprecision. No measures of variability in one study,[58] and wide confidence intervals leading to uncertainty about the true magnitude of the effect in the other.[36]

[d] One prospective cohort study.[62]

[e] Serious risk of bias.[62] Bias due to confounding: significant differences between groups at baseline were not controlled, and treatment arm was assigned by geographical location. Bias in measurement of outcome: diurnal variation was not accounted for in measurement of IOP.

[f] Serious imprecision. Only a single study, and no measures of variability.[62]

[g] One RCT in two publications.[59,60]

[h] Serious risk of bias. Selection bias: no indication of allocation concealment.[59,60] Detection bias: unclear whether diurnal variation accounted for in measurement of IOP.[59,60]

[i] Serious imprecision. Only a single study.[59,60]

[j] In this study, different numbers of iStents (all MIGS) were compared.[59,60]

[k] One non-randomized controlled clinical trial.[61]

[l] Serious risk of bias.[61] Bias due to confounding: pseudorandomization (first patient randomized, followed by counterbalanced enrolment); potential confounding variables not controlled for in analyses. Bias due to missing data: large loss to follow-up, amount of missing data not balanced across groups, and reasons for missing data not reported.

[m] Serious imprecision. Only a single study, and no measures of variability.[61]

Table 34: Effect of MIGS Versus Comparators on Number of Medications in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS Vs. Laser Therapy: Hydrus Microstent Vs. SLT											
1	Prospective cohort[a]	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	None	56	31	**MIGS > Laser Therapy:** The reduction in **number of medications** from baseline at 12 mo follow-up was significantly greater in the Hydrus Microstent vs. SLT (reduction of ~1.4 vs. 0.5 medications, to an average of ~0.9 vs. 2.0 medications, respectively), but absolute number of medications was not compared statistically.[62]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Another MIGS: 1x Vs. 2x Vs. 3x iStent											
1	RCT[d]	Very serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	None	iStent, 38 2x iStent, 41 3x iStent, 40	NA	**3 iStents [?] 2 iStents [?] 1 iStent:** The proportion of eyes requiring medications was numerically reduced from baseline in all groups, but within- and between-group differences were not tested statistically.[59,60]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: ECP Vs. Glaucoma Drainage Device											
2	Retrospective cohort and non-randomized controlled clinical trial[g]	Serious risk of bias[h]	No serious inconsistency	No serious indirectness	No serious imprecision	None	59	BGI, 48 AGI, 34	**MIGS = Glaucoma Drainage Device:** Retrospective cohort study: The mean **number of medications** was significantly reduced from baseline in both ECP and BGI groups at 3 to 24 mo follow-up (reduction of ~1 to 1.5 medications), but was not different between groups at any time point.[63] Non-randomized controlled	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									clinical trial: The **number of medications** was numerically reduced from baseline in both ECP and AGI groups but this was not tested statistically; the mean **number of medications** was not significantly different between groups at baseline or 24 mo follow-up (~2 vs. 2.5 medications, respectively).[61]		
MIGS Vs. Filtration Surgery: Trabectome Vs. Trabeculectomy With MMC											
2	Prospective cohort and retrospective cohort[i]	Serious risk of bias[j]	No serious inconsistency	No serious indirectness	Serious imprecision[k]	None	158	127	**Trabectome < Trabeculectomy With MMC:** Prospective cohort study: The **number of medications** was not reduced from baseline in the Trabectome group at any time point, but was significantly reduced from baseline in the Trabeculectomy group at 1 d to 6 mo follow-up (~2.34 vs. 0.5 medications at 6 mo for Trabectome and Trabeculectomy groups, respectively; between-group comparisons not tested statistically).[25] Retrospective cohort study: The **number of medications** was numerically reduced from baseline in both groups (not tested statistically), but was significantly greater in the Trabectome vs. Trabeculectomy group at all follow-up time points (1 to 30 mo; at 30 mo ~ 2.3 and 0.4 medications, respectively).[64]	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS Vs. Filtration Surgery: 2x istent Inject Vs. Trabeculectomy With MMC											
1	Prospective cohort[l]	Serious risk of bias[m]	No serious inconsistency	No serious indirectness	Serious imprecision[n]	None	20	25	**2x iStent Inject [<] Trabeculectomy With MMC:** The **number of medications** was significantly reduced from baseline in the 2x iStent Inject group at 1 d and 6 wk follow-up, but not 3 or 6 mo follow-up, and was significantly reduced from baseline in the Trebculectomy group at all follow-up time points (at 6 mo: 2.5 vs. 0.5 medications for 2x iStent Inject and Trabeculectomy groups, respectively; between-group differences were not tested statistically).[25]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: Trabectome or 2x istent Inject Vs. Trabeculectomy With MMC											
1	Prospective cohort[l]	Serious risk of bias[m]	No serious inconsistency	No serious indirectness	Serious imprecision[n]	None	63	25	**MIGS < Trabeculectomy with MMC:** The **number of medications** was numerically reduced from baseline in the MIGS group (combined Trabectome and 2x iStent Inject; not tested statistically) and was significantly reduced from baseline in the Trabeculectomy group at 1 d to 6 mo follow-up; the **number of medications** was significantly higher in the MIGS vs. Trabeculectomy groups all follow-up time points .[25]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: Xen45 With MMC Vs. Trabeculectomy With MMC											
1	Retrospective cohort[o]	Serious risk of bias[p]	No serious inconsistency	No serious indirectness	Serious imprecision[q]	None	185	169	**Xen45 with MMC [=] Trabeculectomy with MMC:** The median **number of medications** was numerically similar between Xen45 and Trabeculectomy groups at follow-up (not tested statistically, but median of 0 medications in both groups at median	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									follow-up duration of 15.0 and 17.8 mo, respectively).[65]		

= = not significantly different between groups; [=] = not compared statistically but tendency for no difference between groups; > = intervention more favourable than comparator; < = intervention less favourable than comparator; [<] = not compared statistically but tendency for intervention less favourable than comparator; [?] = not compared statistically or non-interpretable;1x = one device; 2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; BGI = Baerveldt glaucoma implant; d = days; ECP = endoscopic cyclophotocoagulation; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = months; NA = not applicable; no. = number; RCT = randomized controlled trial; SLT = selective laser trabeculoplasty; vs. = versus; wk = weeks; y = years.

Note: Data were collected by RCT, non-randomized controlled clinical trial, retrospective or prospective cohort, with up to 42 months of follow-up. The method of measuring number of medications was not specified in any study.

[a] One prospective cohort study.[62]

[b] Serious risk of bias.[62] Bias due to confounding: significant differences between groups at baseline were not controlled, and treatment arm was assigned by geographical location. Bias in measurement of outcome: method of measuring number of medications not specified. Bias in selection of the reported result: number of medications only reported at 12-month follow-up (other variables also reported at 1, 3, and 6 months).

[c] Serious imprecision. Only a single study, and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).[62]

[d] One RCT in two publications.[59,60]

[e] Very serious risk of bias.[59,60] Selection bias: no indication of allocation concealment. Detection bias: method of measuring number of medications not specified. Reporting bias: absolute number of medications not reported in the results (only the proportion of patients on any medications), and relevant statistical comparisons not conducted or reported.

[f] Serious imprecision. Only a single study, and no measures of variability.[59,60]

[g] One retrospective cohort[63] and one non-randomized controlled clinical trial.[61]

[h] Serious risk of bias.[61,63] Bias due to confounding: different surgeons performed ECP and BGI surgery;[63] pseudorandomization (first patient randomized, followed by counterbalanced enrolment);[61] potential confounding variables not controlled for in analyses.[61,63] Bias in selection of participants: only those with two-year complete data were included and it is possible that those with complete data were systematically different from those without complete data (i.e., different from those in routine clinical practice).[63] Bias due to missing data: large loss to follow-up, amount of missing data not balanced across groups, and reasons for missing data not reported.[61,63] Bias in measurement of outcomes: method of measuring number of medications not specified.[61,63] Bias in selection of the reported result: some preoperative population characteristics that were measured were not reported;[63] number of medications reported only at baseline and 24 months (but at none of the other follow-up time points), and rationale for reporting as medians instead of means not specified.[61]

[i] One prospective cohort[25] and one retrospective cohort study.[64]

[j] Serious risk of bias.[25,64] Bias due to confounding: decision for MIGS versus Trabeculectomy was made by treating surgeon based on patient characteristics, and choice of MIGS was made by individual patients;[25] retrospective study and rationale for assigning treatments likely to be different between groups;[64] significant differences between groups at baseline;[64] potential confounding variables not controlled for in analyses.[25,64] Bias due to missing data: large loss to follow-up and reasons for missing data not reported.[64] Bias in measurement of outcomes: method of measuring number of medications not specified.[25,64]

[k] Serious imprecision. No measures of variability in one study.[25]

[l] One prospective cohort study.[25]

[m] Serious risk of bias.[25] Bias due to confounding: decision for MIGS versus Trabeculectomy was made by treating surgeon based on patient characteristics, and choice of MIGS was made by individual patients; potential confounding variables not controlled for in analyses. Bias in measurement of outcomes: method of measuring number of medications not specified.

[n] Serious imprecision. Only a single study, and no measures of variability.[25]

[o] One retrospective cohort study.[65]

[p] Serious risk of bias.[65] Bias due to confounding: significant differences between groups at baseline; potential confounding variables not controlled for in analyses. Bias in selection of participants: patients with < 1 month follow-up were excluded and it is possible that those with < 1 month follow-up were systematically different from those with ≥ 1 month follow-up (i.e., different from those in routine clinical practice). Bias due to missing data: no information on amount or nature of missing data was reported. Bias in measurement of outcomes: method of measuring number of medications not specified. Bias in selection of the reported result: no rationale for reporting findings as medians instead of means, and absolute values reported only at “last follow-up.”

[q] Serious imprecision. Only a single study.[65]

Table 35: Effect of MIGS Versus Comparators on Visual Field in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS Vs. Pharmacotherapy: 2x iStent Vs. Travoprost											
1	RCT[a]	Very serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	None	2x iStent, 54	Travoprost, 47	**2x iStent [=] Travoprost** **Visual field** (mean deviation and pattern standard deviation) was similar between groups and across time points (baseline through 36 mo follow-up), but this was not tested statistically.[58]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Another MIGS: 1x Vs. 2x Vs. 3x istent											
1	RCT[d]	Very serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	None	iStent, 38 2x iStent, 41 3x iStent, 40	NA[g]	**1 iStent = 2 iStents = 3 iStents:** The **change in visual field** from screening to 42 mo follow-up was not significantly different between groups; whether the absolute visual field was significantly different from screening within groups at 18 or 42 mo follow-up was not tested statistically.[59,60]	⊕OOO VERY LOW	CRITICAL

= = not significantly different between groups; [=] = not compared statistically but tendency for no difference between groups; 2x = two devices; 3x = three devices; MIGS = minimally invasive glaucoma surgery; mo = months; NA = not applicable; no. = number; RCT = randomized controlled trial; vs. = versus.

Note: Data were collected by RCT, with up to 42 months of follow-up. Visual field was measured by Humphrey 24-2 Swedish Interactive Threshold Algorithm, or method of measurement was not reported.

[a] One RCT.[58]

[b] Very serious risk of bias.[58] Selection bias: no indication of allocation concealment. Attrition bias: low-risk at 12- and 24-month follow-up; large amount of missing data at 36-month follow-up and reasons not reported. Reporting bias: no statistical comparisons conducted.

[c] Serious imprecision.[58] Only one study, and no measures of variability.

[d] One RCT in two publications.[59,60]

[e] Very serious risk of bias.[59,60] Selection bias: no indication of allocation concealment. Detection bias: method of measuring visual field not specified. Reporting bias: relevant statistical comparisons not conducted or reported.

[f] Serious imprecision. Only a single study, and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).[59,60]

[g] In this study, different numbers of iStents (all MIGS) were compared.[59,60]

Table 36: Effect of MIGS Versus Comparators on Visual Acuity in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS Vs. Pharmacotherapy: 2x iStent Vs. Travoprost, or 2x iStent Inject Vs. Latanoprost + Timolol											
2	RCT[a]	Very serious risk of bias[b]	No serious inconsistency	Serious indirectness[c]	Serious imprecision[d]	None	2x iStent, 54 2x iStent Inject, 94	Travoprost, 47 Latanoprost + Timolol, 98	**MIGS [?] Pharmacotherapy:** **BCVA:** 2x iStent [?] Travoprost[58] **BCVA:** 2x iStent Inject [?] Latanoprost + Timolol[36]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Laser Therapy: Hydrus Microstent Vs. SLT											
1	Prospective cohort[e]	Serious risk of bias[f]	No serious inconsistency	Serious indirectness[g]	Serious imprecision[h]	None	56	31	**MIGS [=] Laser Therapy:** **Visual acuity** was not significantly different between groups at baseline and was not significantly different from baseline at 12 mo following Hydrus MicroStent or SLT (no between-group statistical comparison).[62]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Another MIGS: 1x Vs. 2x Vs. 3x iStent											
1	RCT[i]	Serious risk of bias[j]	No serious inconsistency	Serious indirectness[k]	Serious imprecision[l]	None	iStent, 38 2x iStent, 41 3x iStent, 40	NA[m]	**1 iStent [=] 2 iStents [=] 3 iStents:** **BCVA** was similar between groups at baseline up to 42 mo follow-up, but this was not tested statistically.[59,60]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: ECP Vs. Glaucoma Drainage Device											
1	Non-randomized controlled clinical trial[n]	Serious risk of bias[o]	No serious inconsistency	Serious indirectness[p]	Serious imprecision[q]	None	34	34	**MIGS = Glaucoma Drainage Device:** **Visual acuity** was not significantly different between ECP and AGI groups at baseline or 12 mo follow-up.[61]	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS Vs. Filtration Surgery: Trabectome Vs. Trabeculectomy With MMC											
2	Prospective cohort and retrospective cohort[r]	Serious risk of bias[s]	No serious inconsistency	Serious indirectness[t]	Serious imprecision[u]	None	158	127	**Mixed Findings; Trabectome [=]/[?] Trabeculectomy with MMC:** Prospective cohort study: **Visual acuity** was numerically similar between groups at baseline or up to 6 mo follow-up, but this was not tested statistically.[25] Retrospective cohort study: **Visual acuity** was not different from baseline at 12 or 24 mo in either group, but was significantly better in the Trabectome vs. Trabeculectomy group at all time points.[64]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: 2x iStent Inject Vs. Trabeculectomy With MMC											
1	Prospective cohort[v]	Serious risk of bias[w]	No serious inconsistency	Serious indirectness[x]	Serious imprecision[y]	None	20	25	**2x iStent Inject [=] Trabeculectomy with MMC:** **Visual acuity** was numerically similar between groups at baseline or up to 6 mo follow-up, but this was not tested statistically.[25]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: Trabectome or 2x iStent Inject Vs. Trabeculectomy With MMC											
1	Prospective cohort[v]	Serious risk of bias[w]	No serious inconsistency	Serious indirectness[x]	Serious imprecision[y]	None	63	25	**MIGS = Trabeculectomy with MMC:** **Visual acuity** was significantly better in MIGS vs. Trabeculectomy at 1 d post-operative, but was not significantly different between groups at any other time point.[25]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: Xen45 With MMC Vs. Trabeculectomy With MMC											
1	Retrospective cohort[z]	Serious risk of bias[aa]	No serious inconsistency	Serious indirectness[bb]	Serious imprecision[cc]	None	185	169	**Xen45 with MMC = Trabeculectomy with MMC:** **Median BCVA** was not significantly different between Xen45 and Trabeculectomy groups at follow-up (median follow-up duration of 15.0 and 17.8 mo respectively).[65]	⊕OOO VERY LOW	CRITICAL

= = not significantly different between groups; [=] = not compared statistically but tendency for no difference between groups; [?] = not compared statistically or non-interpretable; 1x = one device; 2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; BCVA = best-corrected visual acuity; d = days; ECP = endoscopic cyclophotocoagulation; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = months; no. = number; RCT = randomized controlled trial; SLT = selective laser trabeculoplasty; vs. = versus.

Note: Data were collected by RCT, non-randomized controlled clinical trial, retrospective or prospective cohort, with up to 42 months of follow-up. Visual acuity (or best-corrected visual acuity) was measured by decimal chart,[58] or Snellen visual acuities converted to log of the Minimum Angle of Resolution (logMAR);[65] in all other cases the method of measurement was not reported.

[a] Two RCTs.[36,58]

[b] Very serious risk of bias. Selection bias: no indication of allocation concealment.[36,58] Detection bias: method of measurement of BCVA not reported.[36] Attrition bias: low-risk at 12- and 24-month follow-up; large amount of missing data at 36-month follow-up and reasons not reported.[58] Reporting bias: no statistical comparisons conducted[36,58] and values reported for only one of the follow-up time points.[58]

[c] Serious indirectness.[36,58] BCVA only reported as the proportion of eyes with a given BCVA or better; details of BCVA measurement not reported and therefore whether reliable, valid and discriminative (vs. surrogate) measures were used is uncertain.

[d] Serious imprecision.[36,58] No measures of variability.

[e] One prospective cohort study.[62]

[f] Serious risk of bias.[62] Bias due to confounding: significant differences between groups at baseline were not controlled, and treatment arm was assigned by geographical location. Bias in measurement of outcome: method of measurement of visual acuity not reported. Bias in selection of the reported result: relevant statistical comparisons reported at baseline and not reported at follow-up.

[g] Serious indirectness.[62] Method of measuring visual acuity not reported; whether reliable, valid and discriminative (versus surrogate) measures were used is uncertain.

[h] Serious imprecision.[62] Only a single study.

[i] One RCT in two publications.[59,60]

[j] Serious risk of bias.[59,60] Selection bias: no indication of allocation concealment. Detection bias: method of measurement of BCVA not reported. Reporting bias: no statistical comparisons conducted.

[k] Serious indirectness.[59,60] BCVA only reported as the proportion of eyes with a given BCVA or better; details of BCVA measurement not reported and therefore whether reliable, valid, and discriminative (vs. surrogate) measures were used is uncertain.

[l] Serious imprecision.[59,60] Only a single study and no measures of variability.

[m] In this study, different numbers of iStents (all MIGS) were compared.[59,60]

[n] One non-randomized controlled clinical trial.[61]

[o] Serious risk of bias.[61] Bias due to confounding: pseudorandomization (first patient randomized, followed by counterbalanced enrolment); potential confounding variables not controlled for in analyses. Bias due to missing data: large loss to follow-up, amount of missing data not balanced across groups, and reasons for missing data not reported. Bias in measurement of outcomes: sufficient detail regarding method of measuring visual acuity not reported. Bias in selection of the reported result: visual acuity only reported at a subset of measured time points.

[p] Serious indirectness.[61] Sufficient detail of visual acuity measurement not reported and therefore whether reliable, valid, and discriminative (vs. surrogate) measures were used is uncertain.

[q] Serious imprecision.[61] Only a single study.

[r] One prospective cohort[25] and one retrospective cohort study.[64]

[s] Serious risk of bias.[25,64] Bias due to confounding: decision for MIGS versus Trabeculectomy was made by treating surgeon based on patient characteristics, and choice of MIGS was made by individual patients;[25] retrospective study and rationale for assigning treatments likely to be different between groups;[64] significant differences between groups at baseline (including significant difference in visual acuity);[64] potential confounding variables not controlled for in analyses.[25,64] Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups).[25,64] Bias due to missing data: large loss to follow-up and reasons for missing data not reported.[64] Bias in measurement of outcomes: method of measuring visual acuity not reported.[25,64] Bias in selection of the reported result: visual acuity only reported at a subset of measured time points.[64]

[t] Serious indirectness.[25,64] Sufficient detail of visual acuity measurement not reported and therefore whether reliable, valid, and discriminative (versus surrogate) measures were used is uncertain.

[u] Serious imprecision. No measures of variability in one study,[25] and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean) in the other study.[64]

[v] One prospective cohort study.[25]

[w] Serious risk of bias.[25] Bias due to confounding: decision for MIGS versus Trabeculectomy was made by treating surgeon based on patient characteristics, and choice of MIGS was made by individual patients; potential confounding variables not controlled for in analyses. Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias in measurement of outcomes: method of measuring visual acuity not reported.

[x] Serious indirectness.[25] Sufficient detail of visual acuity measurement not reported and therefore whether reliable, valid, and discriminative (versus surrogate) measures were used is uncertain.

[y] Serious imprecision.[25] Only a single study, and no measures of variability.

[z] One retrospective cohort study.[65]

[aa] Serious risk of bias.[65] Bias due to confounding: significant differences between groups at baseline (including significant difference in visual acuity and BCVA); potential confounding variables not controlled for in analyses. Bias in selection of participants: patients with < 1 month follow-up were excluded and it is possible that those with < 1 month follow-up were systematically different from those with ≥ 1 month follow-up (i.e., different from those in routine clinical practice). Bias due to missing data: no information on amount or nature of missing data was reported. Bias in measurement of outcomes: BCVA measured by Snellen visual acuity and converted to logMAR for analysis, which is not considered reliable, valid or discriminative.[96] Bias in selection of the reported result: no rationale for reporting findings as medians instead of means, and absolute values reported only at "last follow-up."

[bb] Serious indirectness.[65] BCVA measured by Snellen visual acuity and converted to logMAR for analysis, which is not considered reliable, valid or discriminative.[96]

[cc] Serious imprecision.[65] Only a single study, and results only presented as medians and inter-quartile ranges.

GRADE Table for Research Question 2

Table 37: Adverse Events and Harms of MIGS Versus Comparators in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS Vs. Pharmacotherapy: 2x iStent Vs. Travoprost, or 2x iStent Inject Vs. Latanoprost + Timolol											
2	RCT[a]	Very serious risk of bias[b]	No serious inconsistency	Serious indirectness[c]	Serious imprecision[d]	None	2x iStent, 54 2x iStent Inject, 94	Travoprost, 47 Latanoprost + Timolol, 98	**MIGS [=] Pharmacotherapy:**[36,58] **Adverse events** were minor in all treatment groups. The incidence of all adverse events was < 2% each[36,58] except for progression of cataract, which was 20% and 17% in *2x* iStent and Travoprost groups respectively in one study.[58]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Laser Therapy: Hydrus Microstent Vs. SLT											
1	Prospective cohort[e]	Serious risk of bias[f]	No serious inconsistency	Serious indirectness[g]	Serious imprecision[h]	None	56	31	**MIGS [=] Laser Therapy:**[62] **Adverse events** were transient (<7 d) and minor in both treatment groups. Adverse event incidence ranged from 6.5% (IOP spike in the Hydrus Microstent group) to 40% (eye discomfort in the SLT group; not reported in the Hydrus Microstent group).[62]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Another MIGS: 1x Vs. 2x Vs. 3x iStent											
1	RCT[i]	Serious risk of bias[j]	No serious inconsistency	Serious indirectness[k]	Serious imprecision[l]	None	iStent, 38 2x iStent, 41 3x iStent, 40	NA[m]	**1 iStent [=] 2 iStents [=] 3 iStents:**[59,60] **Adverse events:** None in any group **Secondary cataract surgery required:** Up to 13% of eyes in each group by 42 mo follow-up; no numerical between-group	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									differences (not tested statistically).		
MIGS Vs. Filtration Surgery: ECP Vs. Glaucoma Drainage Device											
2	Retrospective cohort and non-randomized controlled clinical trial[n]	Serious risk of bias[o]	No serious inconsistency	Serious indirectness[p]	Serious imprecision[q]	None	59	BGI, 48 AGI, 34	**Mixed Findings;[61,63] MIGS =/> Glaucoma Drainage Device:** ***Adverse events:*** No between-group differences[61,63] except for shallow anterior chamber (a minor complication) that occurred in significantly fewer eyes in the ECP vs. AGI group.[61] Major complications (failure of corneal graft, retinal detachment, tube exposure, endophalmitis, phthisis bulbi) occurred in both ECP and AGI groups in one study, with incidence ranging from 2.9% to 11.8%, but with no significant differences between groups.[61]	⊕OOO VERY LOW	CRITICAL
MIGS Vs. Filtration Surgery: Trabectome Vs. Trabeculectomy With MMC											
1	Retrospective cohort[r]	Serious risk of bias[s]	No serious inconsistency	Serious indirectness[t]	Serious imprecision[u]	None	115	102	**Mixed Findings;[64] Trabectome </> Trabeculectomy With MMC:** **Adverse events:** • including hyphema: Trabectome (100%) < Trabeculectomy (~38%) • excluding hyphema: Trabectome (~4%) > Trabeculectomy (~35%) • all minor, except for persistent hypotony (~5% of Trabeculectomy group) and bullous keratopathy (1% of Trabeculectomy group)	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									Secondary glaucoma surgery required: • Trabectome (~44%) < Trabeculectomy (~11%)		
MIGS Vs. Filtration Surgery: Xen45 With MMC Vs. Trabeculectomy With MMC											
1	Retrospective cohort[v]	Serious risk of bias[w]	No serious inconsistency	Serious indirectness[x]	Serious imprecision[y]	None	185	169	**Mixed Findings;[65] Xen45 with MMC [>]/= Trabeculectomy with MMC:** **Adverse events:** • Xen45 (11.9%) [=] Trabeculectomy (17.8%) • Major complications (hypotony maculopathy, corneal decompensation, malignant glaucoma) occurred in both groups, with incidence ranging from 0% to 2.2% across groups; exposed Xen45 occurred in 1 eye (0.5%) **Post-operative interventions:** • Xen45 (63.2%) [>] Trabeculectomy (97.6%) **Secondary glaucoma surgery required:** • Xen45 (10.3%) = Trabeculectomy (5.3%)	⊕OOO VERY LOW	CRITICAL

= = not significantly different between groups; [=] = not compared statistically but tendency for no difference between groups; > = intervention more favourable than comparator; [>] = not compared statistically but tendency for intervention more favourable than comparator; < = intervention less favourable than comparator; 1x = one device; 2x = two devices; 3x = three devices; AGI = Ahmed glaucoma implant; BGI = Baerveldt glaucoma implant; d = days; ECP = endoscopic cyclophotocoagulation; ; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = months; NA = not applicable; no. = number; RCT = randomized controlled trial; SLT = selective laser trabeculoplasty; vs. = versus.

Note: Data were collected by RCT, non-randomized controlled clinical trial, retrospective or prospective cohort, with up to 42 months of follow-up. The method of measuring adverse events or harms was not reported in any study.

[a] Two RCTs.[36,58]

[b] Very serious risk of bias. Selection bias: no indication of allocation concealment.[36,58] Detection bias: method of measuring adverse events and harms not specified.[36,58] Attrition bias: low-risk at 12- and 24 -month follow-up; large amount of missing data at 36-month follow-up and reasons not reported.[58] Reporting bias: no statistical comparisons conducted;[58] no *P* values reported for between-group difference in adverse events.[36]

[c] Serious indirectness.[36,58] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[d] Serious imprecision.[36,58] No measures of variability.

[e] One prospective cohort study.[62]

[f] Serious risk of bias.[62] Bias due to confounding: significant differences between groups at baseline were not controlled, and treatment arm was assigned by geographical location. Bias in measurement of outcome: method of measuring adverse events and harms not specified. Reporting bias: no statistical comparisons conducted.

[g] Serious indirectness.[62] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[h] Serious imprecision.[62] Only a single study and no measures of variability.

[i] One RCT in two publications.[59,60]

[j] Serious risk of bias.[59,60] Selection bias: no indication of allocation concealment. Detection bias: method of measuring adverse events and harms not specified. Reporting bias: no statistical comparisons conducted.

[k] Serious indirectness.[59,60] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[l] Serious imprecision.[59,60] Only a single study; no adverse events or harms, relatively few secondary surgical interventions (all cataract surgery), and no measures of variability.

[m] In this study, different numbers of iStents (all MIGS) were compared.[59,60]

[n] One retrospective cohort[63] and one non-randomized controlled clinical trial.[61]

[o] Serious risk of bias.[61,63] Bias due to confounding: different surgeons performed ECP and BGI surgery;[63] pseudorandomization (first patient randomized, followed by counterbalanced enrolment);[61] potential confounding variables not controlled for in analyses.[61,63] Bias in selection of participants: only those with two-year complete data were included and it is possible that those with complete data were systematically different from those without complete data (i.e., different from those in routine clinical practice).[63] Bias due to missing data: large loss to follow-up, amount of missing data not balanced across groups, and reasons for missing data not reported.[61,63] Bias in measurement of outcomes: method of measuring adverse events and harms not specified.[61,63]

[p] Serious indirectness.[61,63] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[q] Serious imprecision.[61,63] No measures of variability.

[r] One retrospective cohort study.[64]

[s] Serious risk of bias.[64] Bias due to confounding: retrospective study and rationale for assigning treatments likely to be different between groups; significant differences between groups at baseline; potential confounding variables not controlled for in analyses. Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias due to missing data: large loss to follow-up and reasons for missing data not reported; follow-up duration different between groups (i.e., mean follow-up of 7.4 months and 2.1 months in ECP + Phaco and Phaco alone groups, respectively) leading to a different likelihood of capturing adverse events. Bias in measurement of outcomes: method of measuring adverse events and harms not specified.

[t] Serious indirectness.[64] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[u] Serious imprecision.[64] Only a single study and no measures of variability.

[v] One retrospective cohort study.[65]

[w] Serious risk of bias.[65] Bias due to confounding: significant differences between groups at baseline; potential confounding variables not controlled for in analyses. Bias in selection of participants: patients with < 1 month follow-up were excluded and it is possible that those with < 1 month follow-up were systematically different from those with ≥ 1 month follow-up (i.e., different from those in routine clinical practice). Bias due to missing data: no information on amount or nature of missing data was reported. Bias in measurement of outcomes: method of measuring adverse events and harms not specified. Bias in selection of the reported result: statistical comparisons not conducted for adverse events or harms.

[x] Serious indirectness.[65] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[y] Serious imprecision.[65] Only a single study and no measures of variability.

GRADE Tables for Research Question 3

Table 38: Effect of MIGS + Cataract Surgery Versus Comparators on IOP in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: ECP + Phaco Vs. Phaco Alone											
5	Prospective cohort and retrospective cohort[a]	Very serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	555	282	**Mixed Findings; ECP + Phaco =/>/[?] Phaco Alone:** In 3/4 retrospective cohort studies, **IOP** was reduced from baseline in both groups (to ~14 mm Hg to 17.5 mm Hg) but was not different between groups at up to 36 mo follow-up.[73-75] In the fourth retrospective cohort study, IOP was reduced from baseline at mean follow-up of 21 mo in the ECP + Phaco group (to ~14 mm Hg) but was not reported in the Phaco alone group.[72] In the prospective cohort study, **IOP** was significantly reduced from baseline from 6 to 36 mo follow-up but was significantly lower in ECP + Phaco	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									vs. Phaco alone (~15 mm Hg vs. 17 mm Hg at 36 mo respectively).[84]		
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: iStent + Phaco Vs. Phaco Alone											
2	RCTs[c]	Serious risk of bias[d]	Serious inconsistency[e]	No serious indirectness	No serious imprecision	None	129	147	**iStent + Phaco = Phaco Alone: IOP** was not significantly reduced from baseline in either group at 12 to 48 mo follow-up, was significantly lower at both medicated (15 mo) and unmedicated (16 mo) follow-up in the iStent + Phaco vs. Phaco alone groups, but was not different between groups at 48 mo follow-up (~16 mm Hg vs. 17 mm Hg before medication washout respectively).[66,67] **IOP** was numerically similar between groups (~17 mm Hg at 12 and 24 mo follow-up; statistical comparison not reported).[34,68]	⊕⊕OO LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									Meta-analysis results: At 12 mo, mean difference = –0.42 mm Hg, 95% CI, –1.30 to 0.46, $P = 0.34$, $I^2 = 85.47\%$		
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: 2 iStents + Phaco Vs. Phaco Alone											
1	RCT[f]	Serious risk of bias[g]	No serious inconsistency	No serious indirectness	Serious imprecision[h]	None	17	16	**2x iStent + Phaco > Phaco Alone: IOP** was significantly lower in the 2x iStent + Phaco group vs. Phaco alone at 1 to 12 mo follow-up (~2 mm Hg to 4 mm Hg difference between groups).[69]	⊕⊕OO LOW	CRITICAL
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: 1 or 2 iStent(s) + Phaco Vs. Phaco Alone											
1	Retrospective cohort[i]	Very serious risk of bias[j]	No serious inconsistency	No serious indirectness	Serious imprecision[k]	None	iStent + Phaco, 31 2x iStent + Phaco, 22	78	**1 or 2 iStent(s) + Phaco [?] Phaco Alone:** Inconsistent reporting (i.e., different values reported in abstract, tables, and text) so interpretation of findings is unclear.[76]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: CyPass Micro-Stent + Phaco Vs. Phaco Alone											
1	RCT[l]	No serious risk of bias[m]	No serious inconsistency	No serious indirectness	Serious imprecision[n]	None	374	131	**CyPass Micro-Stent + Phaco > Phaco Alone:** The reduction in **IOP** from baseline	⊕⊕⊕O MODERATE	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									was significantly greater in the CyPass Micro-Stent + Phaco vs. Phaco alone group at 12 and 24 mo follow-up (between-group difference in IOP ~2 mm Hg).[70]		
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: Hydrus Microstent + Phaco Vs. Phaco Alone											
2	RCTs[o]	No serious risk of bias[p]	No serious inconsistency	No serious indirectness	No serious imprecision	None	419	237	**Hydrus Microstent + Phaco > Phaco Alone: Diurnal IOP** was reduced from baseline in both groups and was not different between groups at 12 mo follow-up, but was significantly lower in the Hydrus Microstent + Phaco vs. Phaco alone group at 24 mo follow-up (washed-out diurnal IOP ~17 mm Hg vs. 19 mm Hg respectively).[71] The reduction in **modified diurnal IOP** from baseline was significantly greater in the Hydrus Microstent + Phaco vs. Phaco	⊕⊕⊕⊕ HIGH	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									alone group at 12 and 24 mo follow-up (washed-out diurnal IOP ~17 mm Hg vs. 19 mm Hg at 24 mo respectively).[88] Meta-analysis results: At 24 mo, mean difference = –1.87 mm Hg, 95% CI, –2.49 to –1.26, $P < 0.0001$, $I^2 = 0.00\%$		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Goniotomy With KDB + Phaco Vs. iStent + Phaco											
1	Retrospective cohort[q]	Serious risk of bias[r]	No serious inconsistency	No serious indirectness	Serious imprecision[s]	None	KDB + Phaco, 237 iStent + Phaco, 198	NA[t]	**KDB + Phaco > iStent + Phaco: IOP** was significantly reduced from baseline up to 6 mo follow-up in both groups, and the reduction was significantly greater in the KDB + Phaco vs. iStent + Phaco group up to 6 mo follow-up.[86]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Trabectome + Phaco Vs. 2x iStent + Phaco											
2	Retrospective cohort[u]	Serious risk of bias[v]	No serious inconsistency	No serious indirectness	No serious imprecision	None	Trabectome + Phaco, 88 2x iStent + Phaco, 83	NA[t]	**Mixed Findings; Trabectome + Phaco </[?] 2x iStent + Phaco: IOP** was significantly higher	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									in the Trabectome + Phaco versus 2x iStent + Phaco group at baseline and was numerically higher at 12 mo (values shown in figure only) but this did not reach statistical significance.[79] The between-group difference in the reduction in IOP from baseline to 6 mo was inconsistently reported in the paper (i.e., as not significantly different in the text, or as a significantly smaller reduction in the Trabectome + Phaco versus 2x iStent + Phaco group in a figure). **IOP** was significantly reduced from baseline in both groups, but was significantly higher in the Trabectome + Phaco vs. 2x iStent + Phaco group at 6 and 12 mo (~17 mm Hg vs. 14 mm Hg respectively) in			

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									one study.[78] Meta-analysis results: Mean difference = 2.55 mm Hg, 95% CI, 1.44 to 3.66, P < 0.0001, I^2 = 0.00%		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Trabectome + MICS Vs. 2x iStent Inject + MICS											
1	Retrospective cohort[w]	Serious risk of bias[x]	No serious inconsistency	No serious indirectness	Serious imprecision[y]	None	Trabectome + MICS, 25 2x iStent Inject + MICS, 25	NA[t]	**Trabectome + MICS = 2x iStent Inject + MICS: IOP** was significantly reduced from baseline in both groups but was not different between groups up to 12 mo follow-up (values shown in figure only).[77]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Different Numbers of iStents + Phaco											
2	Retrospective cohort and non-randomized controlled clinical trial[z]	Serious risk of bias[aa]	No serious inconsistency	No serious indirectness	No serious imprecision	None	iStent + Phaco, 39 2x iStent + Phaco, 58 3x iStent + Phaco, 25	NA[t]	**1 iStent + Phaco = 2 iStents + Phaco: IOP** was significantly reduced from baseline to 12 mo follow-up (by ~2 to 4 mm Hg), but was not different between groups at any time point.[80] **2 iStents + Phaco = 3 iStents + Phaco:**	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									IOP was significantly reduced from baseline up to 12 mo follow-up (by ~4 mm Hg), but was not different between groups at any time point.[83]		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: ECP + iStent + Phaco Vs. iStent + Phaco											
1	Retrospective cohort[bb]	Serious risk of bias[cc]	No serious inconsistency	No serious indirectness	Serious imprecision[dd]	None	ECP + iStent + Phaco, 51 iStent + Phaco, 50	NA[t]	**ECP + iStent + Phaco > iStent + Phaco:** **IOP** reductions were significantly greater at 12 mo follow-up (mean reductions of 7.14 mm Hg and 4.48 mm Hg, to ~14 mm Hg vs. 16 mm Hg), in ECP + iStent + Phaco vs. iStent + Phaco.[81]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: ECP + Phaco Vs. Trabectome + Phaco											
1	Retrospective cohort[ee]	Serious risk of bias[ff]	No serious inconsistency	No serious indirectness	Serious imprecision[gg]	None	ECP + Phaco, 35 Trabectome + Phaco, 26	NA[t]	**ECP + Phaco = Trabectome + Phaco:** **IOP** was numerically reduced from baseline in both groups up to 12 mo follow-up (by ~3 mm Hg to 4 mm Hg; not tested statistically) and was not significantly	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									different between groups from 1 wk to 12 mo follow-up.[89]		
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery: Trabectome + Phaco Vs. Trabeculectomy With MMC + Phaco											
1	RCT[hh]	Very serious risk of bias[ii]	No serious inconsistency	No serious indirectness	Serious imprecision[jj]	None	10	9	**Trabectome + Phaco = Trabeculectomy + Phaco:** **IOP** was numerically reduced from baseline at 6 and 12 mo of follow-up in both groups (by ~3 mm Hg to 7 mm Hg) but this did not reach statistical significance; **IOP** was not significantly different between groups at baseline or any follow-up time point (at 12 months, ~17 mm Hg in both groups).[87]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery: Trabectome + Phaco Vs. Trabeculotomy + Phaco											
1	Prospective and retrospective cohort[kk]	Serious risk of bias[ll]	No serious inconsistency	No serious indirectness	Serious imprecision[mm]	None	47	29	**Trabectome + Phaco = Trabeculotomy + Phaco:** **IOP** was numerically reduced from baseline from 3 to 36 mo of follow-up in both groups (by	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									~6 mm Hg to 9 mm Hg) but this was not tested statistically; **IOP** was not significantly different between groups at baseline or any follow-up time point (~14 mm Hg at 36 mo in both groups).[85]		
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery: ECP + Phaco Vs. Trabeculectomy With MMC + Phaco											
1	Retrospective cohort[nn]	Serious risk of bias[oo]	No serious inconsistency	No serious indirectness	Serious imprecision[pp]	None	24	29	**ECP + Phaco = Trabeculectomy With MMC + Phaco:** **IOP** was not significantly different between groups at baseline or 6 mo follow-up; IOP was transiently greater post-operative (1 d) in the ECP + Phaco vs. Trabeculectomy + Phaco group.[82]	⊕OOO VERY LOW	CRITICAL

= = not significantly different between groups; > = intervention more favourable than comparator; < = intervention less favourable than comparator; [?] = not compared statistically or non-interpretable; 2x = two devices; CI = confidence interval; d = days; ECP = endoscopic cyclophotocoagulation; IOP = intraocular pressure; KDB = Kahook Dual Blade; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = months; NA = not applicable; no. = number; Phaco = phacoemulsification; RCT = randomized controlled trial; vs. = versus; wk = weeks; y = years.

Note: Data were collected by RCT, non-randomized controlled clinical trial, retrospective or prospective cohort, with up to four years of follow-up. IOP was measured by Goldmann applanation tonometry where reported. The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the Medical Devices Active Licence Listing and is therefore included in this report.

[a] One prospective cohort study[84] and four retrospective cohort studies.[72-75]

[b] Very serious risk of bias. Bias due to confounding: retrospective study and rationale for assigning treatments likely to be different between groups;[72-75] baseline characteristics not reported for Phaco alone group so unable to assess whether groups were systematically different at baseline;[72] treatment assignment based on patient characteristics and groups were systematically different;[73] baseline characteristics (including baseline IOP[73]) were different between groups;[73,74,84] treatment group was assigned based on patient choice and treatment availability;[75] how participants were prospectively assigned to groups was not reported;[84] potential confounding variables not controlled

for in analyses.[72-75,84] Bias in selection of participants: only those with complete data or sufficient follow-up were included and it is possible that those with complete data or a given follow-up duration were systematically different from those without complete data or a particular follow-up duration (i.e., different from those in routine clinical practice);[72,73,84] patients with intraoperative complications were excluded.[74] Bias due to deviations from intended interventions: important co-intervention may not have been balanced between groups (number of medications was not reported in one group;[72] number of medications was inconsistently reported as being significantly different or not significantly different between groups[75]); important co-intervention not balanced between groups (number of medications significantly different between groups). [73,74,84] Bias due to missing data: IOP not reported at baseline or follow-up in the Phaco alone group, and reasons for patient exclusion only reported for the ECP + Phaco group;[72] follow-up duration significantly different between groups (mean of 7.4 vs. 2.1 mo in the ECP + Phaco and Phaco alone groups respectively);[74] low risk up to 24 mo of follow-up but large amount of missing data at later time points and reasons not reported.[84] Bias in measurement of outcomes: diurnal variation was not accounted for in measurement of IOP;[72-75,84] IOP was measured without medication washout and 1) the number of medications was not reported in the Phaco alone group so it is not possible to assess whether this was differentially impacting IOP between groups,[72] 2) the number of medications was not compared statistically between groups,[73] 3) the number of medications was significantly different between groups,[74,84] or 4) number of medications was inconsistently reported as being significantly different or not significantly different between groups.[75] Bias in selection of the reported result: IOP data not reported for Phaco alone group;[72] types of analyses not described in methods and names of statistical tests only reported in table footnotes;[84] reductions from baseline presented only as proportions for IOP but as absolute values for other variables and no rationale reported.[84]

[c] Two RCTs in four publications.[34,66-68]

[d] Serious risk of bias. Selection bias: no indication of allocation concealment.[34,66-68] Detection bias: unclear whether diurnal variation accounted for in measurement of IOP;[34,66-68] no blinding of outcome assessors.[34,68] Attrition bias: low risk up to 15 months of follow-up (reasons for missing data reported and not likely to be related to the outcome), but a large amount of missing data at four year follow-up and amount not balanced across groups;[66,67] large amount of missing data (~9% per group at 12 months and 16% to 18% per group at 24 months), and reasons for missing data may be related to the true outcome (e.g., those with failed Phaco due to adverse event were excluded post-randomization).[34,68] Reporting bias: results not reported comprehensively and rationale for analysis choice not reported (i.e., some results reported with the ITT population and others reported with the "consistent cohort" population); 90% CIs used and no rationale provided (90% CIs are not standard and may have been chosen to narrow the CIs to avoid crossing the line of no effect or to avoid overlap in CIs between groups).[34,68]

[e] Serious inconsistency.[34,66-68] Statistical heterogeneity was substantial.

[f] One RCT.[69]

[g] Serious risk of bias.[69] Selection bias: no indication of allocation concealment. Detection bias: unclear whether diurnal variation accounted for in measurement of IOP; no blinding of outcome assessors.

[h] Serious imprecision.[69] Only a single study.

[i] One retrospective cohort study.[76]

[j] Very serious risk of bias.[76] Bias due to confounding: retrospective study and rationale for assigning treatments likely to be different between groups; potential confounding variables not controlled for in analyses. Bias due to deviations from intended interventions: important co-intervention (number of medications) may not have been balanced across groups. Bias due to missing data: substantial loss to follow-up, reasons for missing data not reported, and amount of missing data not balanced across groups. Bias in measurement of outcomes: method of measurement not reported; diurnal variation not accounted for in measurement of IOP; IOP measured without medication washout and possible that number of medications was different across groups. Bias in selection of the reported result: different numerical values reported in the abstract, tables, and text, leading to unclear interpretation of findings.

[k] Serious imprecision. Only a single study, and no measures of variability.[76]

[l] One RCT.[70]

[m] No serious risk of bias. Only concern was: possible risk of selection bias; no indication of allocation concealment.[70]

[n] Serious imprecision. Only a single study.[70]

[o] Two RCTs.[71,88]

[p] No serious risk of bias. Only concern was: possible risk of selection bias; allocation concealment not explicitly specified but likely, based on method of randomization (online computer algorithms).[71,88]

[q] One retrospective cohort study.[86]

[r] Serious risk of bias.[86] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups; significant differences between groups at baseline; potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with six-month complete data were included and it is possible that those with complete data were systematically different from those without complete data (i.e., different from those in routine clinical practice). Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias due to missing data: large amount of missing data at one month and three months, reasons for missing data not reported, and amount of missing data not balanced across groups. Bias in measurement of outcomes: diurnal variation not accounted for in measurement of IOP; IOP was measured without medication washout and the number of medications was significantly different between groups. Bias in selection of the reported result: *P* value for between-group comparison at baseline not reported.

[s] Serious imprecision.[86] Only a single study.

[t] In these studies, one MIGS performed in combination with cataract surgery was compared with another MIGS combined with cataract surgery.[77-81,83,86]

[u] Two retrospective cohort studies.[78,79]

[v] Serious risk of bias. Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups;[78,79] different surgeons performed procedures in the different treatment arms;[79] only one potential confounding factor controlled for in analyses (i.e., "between-eye correlation" for patients with two eyes in the study);[79] baseline characteristics (including baseline IOP) were different between groups;[79] potential confounding variables not controlled for in analyses.[78] Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice).[78,79] Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups).[78] Bias due to missing data: substantial amount of missing data, amount of missing data not balanced across groups and analyses conducted with last observation carried forward (but disease progression or treatment effectiveness may change over time).[78] Bias in measurement of outcomes: unclear whether diurnal variation was accounted for in measurement of IOP;[78,79] IOP was measured without medication washout and the number of medications was significantly different between groups.[78] Bias in selection of the reported result: inconsistency in reporting of adverse events between abstract, figures, and main text.[79]

[w] One retrospective cohort study.[77]

[x] Serious risk of bias.[77] Bias in selection of participants: only those with complete follow-up were included and it is possible that those with versus without complete follow-up were systematically different (i.e., different from those in routine clinical practice). Bias due to deviations from intended interventions: by design the post-operative medication regimen was different between groups, the number of medications was significantly different between groups at six-week follow-up, and IOP was measured without washout. Bias in measurement of outcomes: unclear whether diurnal variation was accounted for in measurement of IOP; IOP was measured without medication washout and number of medications was significantly different between groups at six-week follow-up.

[y] Serious imprecision.[77] Only a single study.

[z] One retrospective cohort[80] and one non-randomized controlled clinical trial.[83]

[aa] Serious risk of bias. Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups;[80] treatment assigned based on patient characteristics and judgment of operating surgeon (i.e., with those requiring greater IOP control receiving three versus two iStents);[83] potential confounding variables not controlled for in analyses.[80,83] Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice).[83] Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups).[83] Bias due to missing data: substantial loss to follow-up, amount of missing data not balanced across groups, and reasons for missing data not reported.[80] Bias in measurement of outcomes: unclear whether diurnal variation was accounted for in measurement of IOP;[80,83] IOP was measured without medication washout and the number of medications was significantly different between groups.[83]

[bb] One retrospective cohort study.[81]

[cc] Serious risk of bias.[81] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups, groups not matched on baseline characteristics, and potential confounding variables not controlled for in analyses. Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias in measurement of outcomes: unclear whether diurnal variation was accounted for in measurement of IOP; IOP was measured without medication washout and the number of medications was significantly different between groups.

[dd] Serious imprecision.[81] Only a single study; measures of variability only provided at some time points and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).

[ee] One retrospective cohort study.[89]

[ff] Serious risk of bias.[89] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups; some baseline characteristics (e.g., age) different between groups; potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice); at least one patient who did not meet inclusion criteria was included (the inclusion criteria specified age > 40 years, but the range of ages in one group was reported as 30 to 85 years). Bias in measurement of outcomes: unclear whether diurnal variation was accounted for in measurement of IOP.

[gg] Serious imprecision.[89] Only a single study.

[hh] One RCT.[87]

[ii] Very serious risk of bias.[87] Selection bias: inclusion criteria were altered after the start of the study due to slow patient recruitment and specific changes to inclusion criteria were not reported. Performance bias: the study occurred over a long duration and how the intervention (Trabectome + Phaco) was conducted changed over the course of the study (i.e., length of the ablation cleft increased from ~90 to 160 degrees). Detection bias: unclear whether diurnal variation accounted for in measurement of IOP; no blinding of outcome assessors. Attrition bias: only one patient missing data in each group but the sample size was so small that this still represented a substantial proportion of the data (~10% per group). Other bias: the trial was stopped early due to difficulties in patient recruitment and lack of clinical equipoise over time, so fewer participants were recruited than planned a priori.

[jj] Serious imprecision.[87] Only a single study.

[kk] One cohort study; data for one group (Trabeculotomy + Phaco) collected retrospectively and data for the other group (Trabectome + Phaco) collected prospectively.[85]

[ll] Serious risk of bias.[85] Bias due to confounding: data for one group (Trabectome + Phaco) collected retrospectively and data for the other group (Trabeculotomy + Phaco) collected prospectively and it is possible that groups were systematically different; potential confounding variables not controlled for in the analysis. Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice). Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias in measurement of outcomes: unclear whether diurnal variation was accounted for in measurement of IOP; IOP was measured without medication washout and the number of medications was significantly different between groups. Bias due to missing data: substantial amount of missing data, amount of missing data not balanced across groups, and reasons for missing data not reported.

[mm] Serious imprecision. Only a single study.[85]

[nn] One retrospective cohort study.[82]

[pp] Serious risk of bias.[82] Bias due to confounding: participants in the different treatment arms were systematically different; Trabeculectomy + Phaco patients had healthy conjunctiva, ECP + Phaco patients had thin conjunctiva or plateau iris; potential confounding variables not controlled for in the analysis. Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias due to missing data: substantial amount of missing data, amount of missing data not balanced across groups, and reasons for missing data not reported. Bias in measurement of outcomes: unclear whether diurnal variation was accounted for in measurement of IOP; IOP was measured without medication washout and the number of medications was significantly different between groups.

[pp] Serious imprecision. Only a single study; large variability (variability in the estimate similar in magnitude to the parameter).[82]

Table 39: Effect of MIGS + Cataract Surgery Versus Comparators on Proportion of Eyes Achieving IOP Targets

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: CyPass Micro-Stent + Phaco Vs. Phaco Alone											
1	RCT[a]	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	None	374	131	**CyPass Micro-Stent + Phaco > Phaco Alone:** **≥ 20% IOP reduction** from baseline (12 and 24 mo follow-up): • CyPass Micro-Stent + Phaco > Phaco alone[70]	⊕⊕⊕O MODERATE	CRITICAL
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: Hydrus Microstent + Phaco Vs. Phaco Alone											
2	RCTs[d]	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	None	419	237	**Hydrus Microstent + Phaco > Phaco Alone:** **≥ 20% washed-out diurnal IOP reduction** from baseline: • 12 mo follow-up: Hydrus Microstent + Phaco =/> Phaco alone[71,88] • 24 mo follow-up: Hydrus Microstent + Phaco > Phaco alone[71,88] **≥ 30% washed-out diurnal IOP reduction** from baseline: • 24 mo follow-up: Hydrus Microstent + Phaco > Phaco alone[88] **≥ 40% washed-out diurnal IOP reduction** from baseline: • 24 mo follow-up: Hydrus Microstent + Phaco > Phaco alone[88]	⊕⊕⊕O MODERATE	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Goniotomy With KDB + Phaco Vs. iStent + Phaco											
1	Retrospective cohort[g]	Serious risk of bias[h]	No serious inconsistency	No serious indirectness	Serious imprecision[i]	None	KDB + Phaco, 237 iStent	NA[j]	**KDB + Phaco > iStent + Phaco:** **≥ 20% IOP reduction** from baseline (6 mo follow-up):	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
							+ Phaco, 198		• KDB + Phaco > iStent + Phaco[86]		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Different Numbers of iStents + Phaco											
1	Non-randomized controlled clinical trial[k]	Serious risk of bias[l]	No serious inconsistency	No serious indirectness	Serious imprecision[m]	None	2x iStent + Phaco, 28 3x iStent + Phaco, 25	NA[j]	**2 iStents + Phaco [?] 3 iStents + Phaco:** **≤15 mm Hg** (12 mo follow-up): • Only reported in the 2x iStent+Phaco group[83]	⨁OOO VERY LOW	CRITICAL

= = not significantly different between groups; > = intervention more favourable than comparator; [?] = not compared statistically or non-interpretable; 2x = two devices; IOP = intraocular pressure; KDB = Kahook Dual Blade; MIGS = minimally invasive glaucoma surgery; mo = months; NA = not applicable; no. = number; Phaco = phacoemulsification; RCT = randomized controlled trial; vs. = versus.

Note: Data were collected by RCT, non-randomized controlled clinical trial or retrospective cohort, with up to 24 months of follow-up. IOP was measured by Goldmann applanation tonometry where reported. The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the Medical Devices Active Licence Listing and is therefore included in this report.

[a] One RCT.[70]

[b] No serious risk of bias. Only concern was: no indication of allocation concealment.[70]

[c] Serious imprecision. Only a single study.[70]

[d] Two RCTs.[71,88]

[e] No serious risk of bias.[71,88] Only concern was: possible risk of selection bias; concealment not explicitly specified but likely, based on method of randomization (online computer algorithms).

[f] Serious imprecision. In one study, there were wide confidence intervals leading to uncertainty about the true magnitude of the effect and confidence intervals were provided only for the Phaco alone group;[71] in the other study, confidence intervals were only reported for proportion of eyes with ≥ 20% reduction in washed-out modified diurnal IOP but not for ≥ 30% or ≥ 40%.[88]

[g] One retrospective cohort study.[86]

[h] Serious risk of bias.[86] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups; significant differences between groups at baseline; potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with six-month complete data were included and it is possible that those with complete data were systematically different from those without complete data (i.e., different from those in routine clinical practice). Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias due to missing data: large amount of missing data at one month and three months, reasons for missing data not reported, and amount of missing data not balanced across groups. Bias in measurement of outcomes: diurnal variation not accounted for in measurement of IOP; IOP was measured without medication washout and the number of medications was significantly different between groups. Bias in selection of the reported result: no measure of variability.

[i] Serious imprecision.[86] Only a single study and no measure of variability in the proportion of eyes achieving ≥ 20% reduction in IOP.

[j] In these studies, one MIGS performed in combination with cataract surgery was compared with another MIGS combined with cataract surgery.[83,86]

[k] One non-randomized controlled clinical trial.[83]

[l] Serious risk of bias.[83] Bias due to confounding: treatment assigned based on patient characteristics and judgment of operating surgeon (i.e., with those requiring greater IOP control receiving three versus two iStents); potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice). Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias in measurement of outcomes: unclear whether diurnal variation was accounted for in measurement of IOP; IOP was measured without medication washout and the number of medications was significantly different between groups. Bias in selection of the reported result: complete data not reported for the three iStents + Phaco group.

[m] Serious imprecision.[83] Only a single study and no measure of variability.

Table 40: Effect of MIGS + Cataract Surgery Versus Comparators on Number of Medications in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: ECP + Phaco Vs. Phaco Alone											
5	Prospective cohort and retrospective cohort[a]	Very serious risk of bias[b]	Serious inconsistency[c]	No serious indirectness	No serious imprecision	None	555	282	**ECP + Phaco [?] Phaco Alone:** Retrospective cohort studies: In 3/4 retrospective cohort studies[73-75] the **number of medications** was significantly different between groups at baseline; in all cases, comparisons at follow-up tended to favour the group with the higher number of medications at baseline, so interpretation of findings is unclear (2/3 studies[73,74] in favour of ECP + Phaco and 1/3 in favour of Phaco alone[75]). In the fourth retrospective cohort study, the **number of medications** was reduced from baseline at mean follow-up of 21 mo in the ECP + Phaco group but was not reported in the Phaco alone group.[72] Prospective cohort study: The **number of medications** was significantly reduced	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									from baseline to 6 to 36 mo follow-up in both groups (with the exception of 36 mo in Phaco alone) but was significantly lower in ECP + Phaco vs. Phaco alone at baseline and all follow-up time points.[84]		
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: iStent + Phaco Vs. Phaco Alone											
2	RCTs[d]	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	129	147	**iStent + Phaco = Phaco Alone:** The **number of medications** was significantly reduced from baseline in both groups, and was significantly lower in the iStent + Phaco group vs. Phaco alone at 15 mo (~0.4 vs. 1.3 medication, respectively) but not 48 mo (~0.5 vs. 0.9) follow-up in one study, [66,67] and at 12 mo (~0.2 vs. 0.4) but not 24 mo (~0.3 vs. 0.5) follow-up in another study.[34,68] Meta-analysis results: At 12 mo: mean difference = –0.25, 95% CI, –0.52 to 0.01, $P = 0.06$, $I^2 = 17.86\%$	⊕⊕⊕O MODERATE	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: 2 iStents + Phaco Vs. Phaco Alone											
1	RCT[f]	Serious risk of bias[g]	No serious inconsistency	No serious indirectness	Serious imprecision[h]	None	17	16	**2x iStent+Phaco > Phaco Alone:** The **number of medications** was not different between groups up to 2 mo follow-up, but was significantly lower in the 2x iStent + Phaco vs. Phaco alone group at 6 mo (~0.1 vs. 0.5 medications respectively) and 12 mo (~0 vs. 1) follow-up; number of medications was numerically reduced from baseline in both groups but statistical comparison with baseline not conducted.[69]	⊕⊕OO LOW	CRITICAL
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: 1 or 2 iStent(s) + Phaco Vs. Phaco Alone											
1	Retrospective cohort[i]	Very serious risk of bias[j]	No serious inconsistency	No serious indirectness	Serious imprecision[k]	None	iStent + Phaco, 31 2x iStent + Phaco, 22	78	**1 or 2 iStent(s) + Phaco [?] Phaco Alone:** Inconsistent reporting (i.e., different values reported in abstract, tables, and text) so interpretation of findings is unclear.[76]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: CyPass Micro-Stent + Phaco Vs. Phaco Alone											
1	RCT[l]	Serious risk of bias[m]	No serious inconsistency	No serious indirectness	Serious imprecision[n]	None	374	131	**CyPass Micro-Stent + Phaco > Phaco Alone:** There were significantly fewer	⊕⊕OO LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									medications required in the CyPass Micro-Stent + Phaco vs. Phaco alone group at 12 (~0.2 vs. 0.7 medications, respectively) and 24 mo follow-up ("maintained" vs. 0.6); statistical comparison with baseline not conducted.[70]		
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: Hydrus Microstent + Phaco Vs. Phaco Alone											
2	RCTs[o]	Serious risk of bias[p]	No serious inconsistency	No serious indirectness	Serious imprecision[q]	None	419	237	**Hydrus Microstent + Phaco > Phaco Alone:** The **number of medications** was significantly reduced from baseline in both groups and was lower in the Hydrus Microstent + Phaco vs. Phaco alone group at 24 mo follow-up (~0.5 vs. 1.0 respectively).[71]The **reduction in number of medications** from baseline to 24 mo follow-up was significantly greater in the Hydrus Microstent + Phaco vs. Phaco alone group (~1.4 vs. 1.0 medications respectively).[88] Meta-analysis results: At 24 mo, mean	⊕⊕OO LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									difference = –0.41, 95% CI, –0.56 to –0.27, *P* < 0.0001, I^2 = 0.00%		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Goniotomy With KDB + Phaco Vs. iStent + Phaco											
1	Retrospective cohort[r]	Serious risk of bias[s]	No serious inconsistency	No serious indirectness	Serious imprecision[t]	None	KDB + Phaco, 237 iStent + Phaco, 198	NA[u]	**KDB + Phaco > iStent + Phaco:** The **number of medications** was significantly lower, and the reduction in medications from baseline significantly greater, in the KDB + Phaco vs. iStent + Phaco group at 1, 3, and 6 mo follow-up.[86]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Trabectome + Phaco Vs. 2 iStents + Phaco											
2	Retrospective cohort[v]	Serious risk of bias[w]	Serious inconsistency[x]	No serious indirectness	No serious imprecision	None	Trabectome + Phaco, 88 iStent + Phaco, 83	NA[u]	**Trabectome + Phaco = 2x iStent + Phaco:** The absolute **number of medications** was not significantly different between groups at baseline or 6 or 12 mo follow-up, but the **reduction in number of medications** from baseline was significantly greater in Trabectome + Phaco vs. iStent + Phaco group at 6 mo but not 12 mo follow-up.[79] The **median number of medications** was significantly reduced from baseline in both	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									groups, but was significantly higher in the Trabectome + Phaco vs. 2x iStent + Phaco group at 3, 6, and 12 mo follow-up (~1 vs. 2 medications respectively).[78] Meta-analysis results: At 12 mo: mean difference = 0.41 medications, 95% CI, -0.65 to 1.46, *P* = 0.4521, I^2 = 85.33%		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Trabectome + MICS Vs. 2x iStent Inject + MICS											
1	Retrospective cohort[y]	Serious risk of bias[z]	No serious inconsistency	No serious indirectness	Serious imprecision[aa]	None	Trabectome + MICS, 25 2x iStent Inject + MICS, 25	NA[u]	**Trabectome + MICS = 2x iStent Inject + MICS:** The **number of medications** was significantly reduced from baseline in both groups but was not different between groups up to 12 mo follow-up (~1.4 vs. 1.3 medications for Trabectome + MICS and 2x iStent Inject + MICS, respectively).[77]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Different Numbers of iStents + Phaco											
2	Retrospective cohort and non-randomized controlled clinical trial[bb]	Serious risk of bias[cc]	No serious inconsistency	No serious indirectness	No serious imprecision	None	iStent + Phaco, 39 2x iStent + Phaco, 58 3x iStent +	NA[u]	**1 iStent + Phaco = 2 iStents + Phaco:** At 12 mo follow-up, the **number of medications** was significantly reduced from baseline only in	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
							Phaco, 25		the 2x iStent + Phaco group, and the **number of medications** was not significantly different between groups at any time point (at 12 mo follow-up, ~1.7 vs. 1.2 medications for 1 vs. 2 iStent groups, respectively).[80] **2 iStents + Phaco < 3 iStents + Phaco:** The **number of medications** was significantly reduced from baseline at 12 mo follow-up in both groups, and was significantly higher in the 2x iStent + Phaco vs. 3x iStent + Phaco group at 6 mo (~1.2 vs. 0.4 medications, respectively) and 12 mo (~1.0 vs. 0.4 medications) follow-up.[83]		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: ECP + iStent + Phaco Vs. iStent + Phaco											
1	Retrospective cohort[dd]	Serious risk of bias[ee]	No serious inconsistency	No serious indirectness	Serious imprecision[ff]	None	ECP + iStent + Phaco, 51 iStent + Phaco, 50	NA[u]	**ECP + iStent + Phaco < iStent + Phaco:** The **number of medications** was significantly greater at 12 mo follow-up in ECP + iStent + Phaco vs. iStent + Phaco (~1.1 vs. 0.62	⨁OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									medications, respectively).[81]		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: ECP + Phaco Vs. Trabectome + Phaco											
1	Retrospective cohort[gg]	Serious risk of bias[hh]	No serious inconsistency	No serious indirectness	Serious imprecision[ii]	None	ECP + Phaco, 35 Trabectome + Phaco, 26	NA[u]	**ECP + Phaco = Trabectome + Phaco:** The **number of medications** was not significantly different between groups at baseline or any follow-up time point.[89]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery: Trabectome + Phaco Vs. Trabeculectomy With MMC + Phaco											
1	RCT[jj]	Very serious risk of bias[kk]	No serious inconsistency	No serious indirectness	Serious imprecision[ll]	None	10	9	**Trabectome + Phaco = Trabeculectomy + Phaco:** The **number of medications** was numerically reduced from baseline at 6 and 12 mo of follow-up in both groups (by ~1 medication) but this did not reach statistical significance; **number of medications** was not significantly different between groups at baseline or any follow-up time point.[87]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery: Trabectome + Phaco Vs. Trabeculotomy + Phaco											
1	Prospective and retrospective cohort[mm]	Serious risk of bias[nn]	No serious inconsistency	No serious indirectness	Serious imprecision[oo]	None	47	29	**Trabectome + Phaco = Trabeculotomy + Phaco:** The **number of medications** was significantly greater in the Trabectome +	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									Phaco vs. Trabeculotomy + Phaco group at 3, 6, and 12 mo follow-up, but was not different between groups at 18, 24, or 26 mo.[85]		
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery: ECP + Phaco Vs. Trabeculectomy With MMC + Phaco											
1	Retrospective cohort[pp]	Serious risk of bias[qq]	No serious inconsistency	No serious indirectness	Serious imprecision[rr]	None	24	29	**ECP + Phaco < Trabeculectomy With MMC + Phaco:** The **number of medications** was not different between groups at baseline but was significantly higher in the ECP + Phaco vs. Trabeculectomy + Phaco group at 6 mo follow-up (~1.4 vs. 0.5 medications, respectively).[82]	⊕OOO VERY LOW	CRITICAL

= = not significantly different between groups; > = intervention more favourable than comparator; < = intervention less favourable than comparator; [?] = not compared statistically or non-interpretable; 2x = two devices; 3x = three devices; CI = confidence interval; d = days; ECP = endoscopic cyclophotocoagulation; IOP = intraocular pressure; KDB = Kahook Dual Blade; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = months; NA = not applicable; no. = number; Phaco = phacoemulsification; RCT = randomized controlled trial; vs. = versus; wk = weeks; y = years.

Note: Data were collected by RCT, non-randomized controlled clinical trial, retrospective or prospective cohort, with up to four years of follow-up. The method of measuring number of medications was not specified in any study. The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the Medical Devices Active Licence Listing and is therefore included in this report.

[a] One prospective cohort study[84] and four retrospective cohort studies.[72-75]

[b] Very serious risk of bias. Bias due to confounding: retrospective study and rationale for assigning treatments likely to be different between groups;[72-75] baseline characteristics not reported for the Phaco alone group so unable to assess whether groups were systematically different at baseline;[72] treatment assignment based on patient characteristics and groups were systematically different;[73] baseline characteristics were different between groups;[73,74,84] number of medications was significantly different between groups at baseline[73,74,84] (possibly also significantly different between groups at baseline in the study by Siegel et al. 2015;[75] however, this was inconsistently reported throughout the paper); treatment group was assigned based on patient choice and treatment availability;[75] how participants were prospectively assigned to groups was not reported;[84] potential confounding variables not controlled for in analyses.[72-75,84] Bias in selection of participants: only those with complete data or sufficient follow-up were included and it is possible that those with complete data or a given follow-up duration were systematically different from those without complete data or a particular follow-up duration (i.e., different from those in routine clinical practice);[72,73,84] patients with intraoperative complications were excluded.[74] Bias due to missing data: number of medications not reported at baseline or follow-up in the Phaco alone group, and reasons for patient exclusion only reported for the ECP + Phaco group;[72] follow-up duration significantly different between groups (mean of 7.4 vs. 2.1 mo in the ECP + Phaco and Phaco alone groups respectively);[74] low risk up to 24 mo of follow-up but large amount of missing data at later time points and reasons not reported.[84] Bias in measurement of outcomes: method of measuring number of medications not specified.[72-75,84] Bias in selection of the reported result: number of medications not reported for Phaco alone group;[72] number of medications was not compared statistically between groups;[73]

inconsistent reporting of *P* values for between-group comparison of baseline number of medications (non-significant and significant values reported in study Tables 1 and 2, respectively) so interpretation of findings is unclear;[75] types of analyses not described in methods and names of statistical tests only reported in table footnotes.[84]

[c] Serious inconsistency. Unexplained heterogeneity in the direction of the effect.

[d] Two RCTs in four publications.[34,66-68]

[e] Serious risk of bias. Selection bias: no indication of allocation concealment.[34,66-68] Detection bias: method of measuring number of medications not specified.[34,66-68] Attrition bias: low-risk up to 15 months of follow-up (reasons for missing data reported and not likely to be related to the outcome), but large amount of missing data at four year follow-up and amount not balanced across groups;[66,67] large amount of missing data (~9% per group at 12 months and 16% to 18% per group at 24 months), and reasons for missing data may be related to the true outcome (e.g., those with failed Phaco due to adverse event were excluded post-randomization).[34,68] Reporting bias: results not reported comprehensively and rationale for analysis choice not reported (i.e., some results reported with the intention-to-treat population and others reported with the "consistent cohort" population); 90% CIs used and no rationale provided (90% CIs are not standard and may have been chosen to narrow the CIs to avoid crossing the line of no effect or to avoid overlap in CIs between groups).[34,68]

[f] One RCT.[69]

[g] Serious risk of bias.[69] Selection bias: no indication of allocation concealment. Detection bias: method of measuring number of medications not specified.

[h] Serious imprecision.[69] Only a single study.

[i] One retrospective cohort study.[76]

[j] Very serious risk of bias.[76] Bias due to confounding: retrospective study and rationale for assigning treatments likely to be different between groups; potential confounding variables not controlled for in analyses. Bias due to missing data: substantial loss to follow-up, reasons for missing data not reported, and amount of missing data not balanced across groups. Bias in measurement of outcomes: method of measuring number of medications not specified. Bias in selection of the reported result: number of medications was not compared statistically between groups; different numerical values reported in the abstract, tables, and text, leading to unclear interpretation of findings.

[k] Serious imprecision. Only a single study, and no measures of variability.[76]

[l] One RCT.[70]

[m] Serious risk of bias.[70] Selection bias: no indication of allocation concealment. Detection bias: method of measuring number of medications not specified.

[n] Serious imprecision. Only a single study.[70]

[o] Two RCTs.[71,88]

[p] Serious risk of bias. [71,88] Possible risk of selection bias; concealment not explicitly specified but likely, based on method of randomization (online computer algorithms). Detection bias: method of measuring number of medications not specified.

[q] Serious imprecision. Variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean),[71] or no measure of variability was reported.[88]

[r] One retrospective cohort study.[86]

[s] Serious risk of bias.[86] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups; significant differences between groups at baseline; potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with six months of complete data were included and it is possible that those with complete data were systematically different from those without complete data (i.e., different from those in routine clinical practice). Bias due to missing data: large amount of missing data at one month and three months, reasons for missing data not reported, and amount of missing data not balanced across groups. Bias in measurement of outcomes: method of measuring number of medications not specified.

[t] Serious imprecision.[86] Only a single study.

[u] In these studies, one MIGS performed in combination with cataract surgery was compared with another MIGS combined with cataract surgery.[77-81,83,86]

[v] Two retrospective cohort studies.[78,79]

[w] Serious risk of bias. Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups;[78,79] different surgeons performed procedures in the different treatment arms;[79] only one potential confounding factor controlled for in analyses (i.e., "between-eye correlation" for patients with two eyes in the study);[79] potential confounding variables not controlled for in analyses.[78] Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice).[78,79] Bias due to missing data: substantial amount of missing data, amount of missing data not balanced across groups and analyses conducted with last observation carried forward (but disease progression or treatment effectiveness may change over time).[78] Bias in measurement of outcomes: method of measuring number of medications not specified.[78,79]

[x] Serious inconsistency.[78,79] Substantial statistical heterogeneity.

[y] One retrospective cohort study.[77]

[z] Serious risk of bias.[77] Bias in selection of participants: only those with complete follow-up were included and it is possible that those with versus without complete follow-up were systematically different (i.e., different from those in routine clinical practice). Bias in measurement of outcomes: method of measuring number of medications not specified.

[aa] Serious imprecision.[77] Only a single study, and variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).

[bb] One retrospective cohort[80] and one non-randomized controlled clinical trial.[83]

[cc] Serious risk of bias. Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups;[80] treatment assigned based on patient characteristics and judgment of operating surgeon (i.e., with those requiring greater IOP control receiving three versus two iStents);[83] potential confounding variables not controlled for in analyses.[80,83] Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice).[83] Bias due to missing data: substantial loss to follow-up, amount of missing data not balanced across groups, and reasons for missing data not reported.[80] Bias in measurement of outcomes: method of measuring number of medications not specified.[80,83]

[dd] One retrospective cohort study.[81]

[ee] Serious risk of bias.[81] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups, groups not matched on baseline characteristics, and potential confounding variables not controlled for in analyses. Bias in measurement of outcomes: method of measuring number of medications not specified.

[ff] Serious imprecision.[81] Only a single study; measures of variability only provided at some time points, only for the intervention (ECP + iStent + Phaco) but not comparator (iStent + Phaco) group at 12-month follow-up, and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).

[gg] One retrospective cohort study.[89]

[hh] Serious risk of bias.[89] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups; some baseline characteristics (e.g., age) different between groups; potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice); at least one patient who did not meet inclusion criteria was included (the inclusion criteria specified age > 40 years, but the range of ages in one group was reported as 30 to 85 years). Bias in measurement of outcomes: method of measuring number of medications not specified.

[ii] Serious imprecision.[89] Only a single study and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).[89]

[jjg] One RCT.[87]

[kk] Very serious risk of bias.[87] Selection bias: inclusion criteria were altered after the start of the study due to slow patient recruitment and specific changes to inclusion criteria were not reported. Performance bias: the study occurred over a long duration and how the intervention (Trabectome + Phaco) was conducted changed over the course of the study (i.e., length of the ablation cleft increased from ~90 to 160 degrees). Detection bias: method of measuring number of medications not specified. Attrition bias: only one patient missing data in each group but the sample size was so small that this still represented a substantial proportion of the data (~10% per group). Other bias: the trial was stopped early due to difficulties in patient recruitment and lack of clinical equipoise over time, so fewer participants were recruited than planned a priori.

[ll] Serious imprecision.[87] Only a single study and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).[87]

[mm] One cohort study; data for one group (Trabectome + Phaco) collected retrospectively and data for the other group (Trabeculotomy + Phaco) collected prospectively.[85]

[nn] Serious risk of bias.[85] Bias due to confounding: data for one group (Trabeculotomy + Phaco) collected retrospectively and data for the other group (Trabectome + Phaco) collected prospectively and it is possible that groups were systematically different; potential confounding variables not controlled for in the analysis. Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice). Bias in measurement of outcomes: method of measuring number of medications not specified. Bias due to missing data: substantial amount of missing data, amount of missing data not balanced across groups, and reasons for missing data not reported.

[oo] Serious imprecision. Only one study.[85]

[pp] One retrospective cohort study.[82]

[qq] Serious risk of bias.[82] Bias due to confounding: participants in the different treatment arms were systematically different; Trabeculectomy + Phaco patients had healthy conjunctiva, ECP + Phaco patients had thin conjunctiva or plateau iris; potential confounding variables not controlled for in the analysis. Bias due to missing data: substantial amount of missing data, amount of missing data not balanced across groups, and reasons for missing data not reported. Bias in measurement of outcomes: method of measuring number of medications not specified.

[rr] Serious imprecision. Only a single study; large variability (variability in the estimate similar in magnitude to the parameter).[82]

Table 41: Effect of MIGS + Cataract Surgery Versus Comparators on Visual Field in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: iStent + Phaco Vs. Phaco Alone											
1	RCT[a]	Very serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	None	117	123	**iStent + Phaco = Phaco Alone: Visual field** (mean deviation and pattern standard deviation) was not significantly different between groups at baseline or 24 mo follow-up; within-group comparison from baseline to follow-up not tested statistically.[34,68]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: ECP + Phaco Vs. Trabectome + Phaco											
1	Retrospective cohort[d]	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	None	ECP + Phaco, 35 Trabectome + Phaco, 26	NA[g]	**ECP + Phaco = Trabectome + Phaco:** The mean change in **visual field** from baseline to 12 mo follow-up was not significantly different between groups.[89]	⊕OOO VERY LOW	CRITICAL

= = not significantly different between groups; MIGS = minimally invasive glaucoma surgery; mo = months; no. = number; Phaco = phacoemulsification; RCT = randomized controlled trial; vs. = versus.

Note: Data were collected by RCT, with up to 24 months of follow-up. Visual field was measured by Humphrey 30-2 or 24-2 Swedish Interactive Threshold Algorithm standard.

[a] One RCT in two publications.[34,68]

[b] Very serious risk of bias.[34,68] Selection bias: no indication of allocation concealment. Detection bias: no blinding of outcome assessors. Attrition bias: large amount of missing data (~9% per group at 12 months and 16% to 18% per group at 24 months), and reasons for missing data may be related to the true outcome (e.g., those with failed Phaco due to adverse event were excluded post-randomization). Reporting bias: results not reported comprehensively and rationale for analysis choice not reported (i.e., some results reported with the intention-to-treat population and others reported with the "consistent cohort" population); visual field results reported only at baseline and 24-month follow-up time points.

[c] Serious imprecision.[34,68] Only a single study, and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).

[d] One retrospective cohort study.[89]

[e] Serious risk of bias.[89] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups; some baseline characteristics (e.g., age) different between groups; potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice); at least one patient who did not meet inclusion criteria was included (the inclusion criteria specified age > 40 years, but the range of ages in one group was reported as 30 to 85 years). Bias in selection of the reported result: visual field was not included in the methods as an outcome measure but was included as such in the results.

[f] Serious imprecision.[89] Only a single study, and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).

[g] In this study, one MIGS performed in combination with cataract surgery was compared with another MIGS combined with cataract surgery.[89]

Table 42: Effect of MIGS + Cataract Surgery Versus Comparators on Visual Acuity in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. Of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: ECP + Phaco Vs. Phaco Alone											
4	Retrospective cohort[a]	Very serious risk of bias[b]	No serious inconsistency	Serious indirectness[c]	Serious imprecision[d]	None	475	202	**ECP + Phaco =/[=] Phaco Alone: VA**[72,73,75] and **BCVA**[74] were not different[74,75] between groups (or were numerically similar; no statistical comparisons[72,73]) at baseline or up to 36 mo follow-up.	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: iStent + Phaco Vs. Phaco Alone											
1	RCT[e]	Serious risk of bias[f]	No serious inconsistency	Serious indirectness[g]	Serious imprecision[h]	None	117	123	**iStent + Phaco [=] Phaco Alone: CDVA** was numerically similar between groups at baseline, 12 and 24 mo follow-up, but this was not tested statistically.[34,68]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: 1 or 2 iStents + Phaco Vs. Phaco Alone											
1	Retrospective cohort[i]	Serious risk of bias[j]	No serious inconsistency	Serious indirectness[k]	Serious imprecision[l]	None	iStent + Phaco, 31 2x iStent + Phaco, 22	78	**1 or 2 iStent(s) + Phaco [?] Phaco Alone:** Inconsistent reporting (i.e., different values reported in abstract, tables, and text) so interpretation of findings is unclear.[76]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Goniotomy With KDB + Phaco Vs. iStent + Phaco											
1	Retrospective cohort[m]	Serious risk of bias[n]	No serious inconsistency	Serious indirectness[o]	Serious imprecision[p]	None	KDB + Phaco, 237 iStent + Phaco, 198	NA[q]	**KDB + Phaco = iStent + Phaco: BCVA** improved significantly from baseline to 6 mo in both groups, and the change in BCVA was not significantly different between groups.[86]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Trabectome + Phaco Vs. 2x iStent + Phaco											
1	Retrospective cohort[r]	Serious risk of bias[s]	No serious inconsistency	Serious indirectness[t]	Serious imprecision[u]	None	Trabectome + Phaco, 36 2x iStent + Phaco, 34	NA[q]	**Trabectome + Phaco = 2x iStent + Phaco:** **BCVA** was not significantly different between groups at baseline, and the change from baseline to 12 mo follow-up was not significantly different between groups.[79]	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. Of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Trabectome + MICS Vs. 2x iStent Inject + MICS											
1	Retrospective cohort[v]	Serious risk of bias[w]	No serious inconsistency	Serious indirectness[x]	Serious imprecision[y]	None	Trabectome + MICS, 25 2x iStent Inject + MICS, 25	NA[q]	**Trabectome + MICS = 2x iStent Inject + MICS:** **BCVA** was improved from baseline at 12 mo follow-up in both groups, with no significant difference between groups at any time point.[77]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Different Numbers of iStents + Phaco											
1	Non-randomized controlled clinical trial[z]	Serious risk of bias[aa]	No serious inconsistency	Serious indirectness[bb]	Serious imprecision[cc]	None	2x iStent + Phaco, 28 3x iStent + Phaco, 25	NA[q]	**2 iStents + Phaco [=] 3 iStents + Phaco:** The proportion of eyes with a given **CDVA** was not different between groups at baseline and was numerically similar at 12 mo follow-up, but this was not tested statistically.[83]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery: ECP + Phaco Vs. Trabeculectomy With MMC + Phaco											
1	Retrospective cohort[dd]	Serious risk of bias[ee]	No serious inconsistency	Serious indirectness[ff]	Serious imprecision[gg]	None	24	29	**ECP + Phaco = Trabeculectomy with MMC + Phaco:** **VA** was significantly improved from baseline at 6 mo follow-up in both groups and was not significantly different between groups.[82]	⊕OOO VERY LOW	CRITICAL

= = not significantly different between groups; [=] = not compared statistically but tendency for no difference between groups; 2x = two devices; 3x = three devices; BCVA = best-corrected visual acuity; CDVA = corrected-distance visual acuity; ECP = endoscopic cyclophotocoagulation; KDB = Kahook Dual Blade; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = months; NA = not applicable; no. = number; Phaco = phacoemulsification; RCT = randomized controlled trial; VA = visual acuity; vs. = versus.

Note: Data were collected by RCT, non-randomized controlled clinical trial, or retrospective cohort, with up to 36 months (three years) of follow-up. Visual acuity, BCVA or CDVA were measured by Snellen visual acuity or eye chart[72,75,79,83] or Snellen converted to logMAR;[73,74,82,86] in all other cases the method of measurement was not reported.

[a] Four retrospective cohort studies.[72-75]

[b] Very serious risk of bias. Bias due to confounding: retrospective study and rationale for assigning treatments likely to be different between groups;[72-75] baseline characteristics not reported for the Phaco alone group so unable to assess whether groups were systematically different at baseline;[72] treatment assignment based on patient characteristics and groups were systematically different;[73] baseline characteristics were different between groups;[73,74] treatment group was assigned based on patient choice and treatment availability;[75] potential confounding variables not controlled for in analyses.[72-75] Bias in selection of participants: only those with complete data or sufficient follow-up were included and it is possible that those with complete data or a given follow-up duration were systematically different from those without complete data or a particular follow-up duration (i.e., different from those in routine clinical practice);[72,73] patients with intraoperative complications were excluded.[74] Bias due to deviations from intended interventions: important co-intervention may not have been balanced between groups (number of medications was not reported in one group;[72] absolute number of medications not compared statistically between groups[73]); important co-intervention not balanced between groups (number of medications significantly different between groups).[74,75] Bias due to missing data: reasons for patient exclusion only reported for the ECP + Phaco group;[72] follow-up duration significantly different between groups (mean of 7.4 versus 2.1 months in the ECP + Phaco and Phaco alone groups, respectively).[74] Bias in measurement of outcomes: visual acuity measured by Snellen[72,75] or Snellen converted to logarithm of the minimum angle of resolution (logMAR),[73,74] which are not considered reliable, valid, or discriminative measures.[96] Bias in selection of the reported result: VA only reported as the proportion of eyes with improved, same, or worsened VA and not as absolute values;[72] VA only reported at baseline and one-month follow-up (while other variables were assessed at follow-up ranging from 1 to 43.4 months);[74] VA only reported at baseline and the last follow-up time point.[75]

[c] Serious indirectness.[72-75] VA or BCVA measured by Snellen or Snellen converted to logMAR for analysis, which is not considered reliable, valid or discriminative.[96]

[d] Serious imprecision.[72,74,75] VA only reported as the proportion of eyes with improved, same, or worsened VA and not as absolute values;[72] no measures of variability. [72,74,75]

[e] One RCT in two publications.[34,68]

[f] Serious risk of bias.[34,68] Selection bias: no indication of allocation concealment.[34,68] Detection bias: method of measurement of CDVA not reported. Attrition bias: large amount of missing data (~9% per group at 12 months and 16% to 18% per group at 24 months), and reasons for missing data may be related to the true outcome (e.g., those with failed Phaco due to adverse event were excluded post-randomization). Reporting bias: results not reported comprehensively and rationale for analysis choice not reported (i.e., some results reported with the intention-to-treat population and others reported with the "consistent cohort" population); different breakdown of CDVA reported at baseline and 24-month follow-up.[34,68]

[g] Serious indirectness.[34,68] Sufficient detail of measuring CDVA not reported and therefore whether reliable, valid and discriminative (versus surrogate) measures were used is uncertain.

[h] Serious imprecision.[34,68] Only a single study, no measures of variability, and CDVA only reported as the proportion of eyes with a given CDVA or better.

[i] One retrospective cohort study.[76]

[j] Very serious risk of bias.[76] Bias due to confounding: retrospective study and rationale for assigning treatments likely to be different between groups; potential confounding variables not controlled for in analyses. Bias due to deviations from intended interventions: important co-intervention (number of medications) may not have been balanced across groups. Bias due to missing data: substantial loss to follow-up, reasons for missing data not reported, and amount of missing data not balanced across groups. Bias in measurement of outcomes: method of measurement not reported. Bias in selection of the reported result: units for VA not specified and values only reported at baseline.

[k] Serious indirectness.[76] No detail regarding measurement of VA reported, and therefore whether reliable, valid, and discriminative (versus surrogate) measures were used in uncertain.

[l] Serious imprecision.[76] Only a single study and no measures of variability.

[m] One retrospective cohort study.[86]

[n] Serious risk of bias.[86] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups; significant differences between groups at baseline; potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with six-month complete data were included and it is possible that those with complete data were systematically different from those without complete data (i.e., different from those in routine clinical practice). Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias due to missing data: large amount of missing data at one month and three months, reasons for missing data not reported, and amount of missing data not balanced across groups. Bias in measurement of outcomes: BCVA measured by Snellen converted to logMAR, which is not considered a reliable, valid, or discriminative measure.[96] Bias in selection of the reported result: BCVA only reported pooled across groups and only at baseline and six-month follow-up.

[o] Serious indirectness.[86] BCVA measured by Snellen converted to logMAR for analysis, which is not considered reliable, valid, or discriminative.[96]

[p] Serious imprecision.[86] Only a single study, and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).

[q] In these studies, one MIGS performed in combination with cataract surgery was compared with another MIGS combined with cataract surgery.[77,79,83,86]

[r] One retrospective cohort study.[79]

[s] Serious risk of bias.[79] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups; different surgeons performed procedures in the different treatment arms; only one potential confounding factor controlled for in analyses (i.e., "between-eye correlation" for patients with two eyes in the study). Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice). Bias in measurement of outcomes: visual acuity measured by Snellen, which is not considered a reliable, valid, or discriminative measure.[96] Bias in selection of the reported result: BCVA only presented as change from baseline and not as absolute values, and only reported for 12-month follow-up time point.

[t] Serious indirectness.[79] BCVA measured by Snellen, which is not considered reliable, valid, or discriminative.[96]

[u] Serious imprecision.[79] Only a single study and no measures of variability.

[wv] One retrospective cohort study.[77]

[w] Serious risk of bias.[77] Bias in selection of participants: only those with complete follow-up were included and it is possible that those with versus without complete follow-up were systematically different (i.e., different from those in routine clinical practice). Bias due to deviations from intended interventions: by design the post-operative medication regimen was different between groups, the number of medications was significantly different between groups at six-week follow-up, and intraocular pressure was measured without washout. Bias in measurement of outcomes: method of measuring BCVA not reported.

[x] Serious indirectness.[77] Sufficient detail of measuring BCVA not reported and therefore whether reliable, valid, and discriminative (versus surrogate) measures were used is uncertain.

[y] Serious imprecision.[77] Only a single study, and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).

[z] One non-randomized controlled clinical trial.[83]

[aa] Serious risk of bias.[83] Bias due to confounding: treatment assigned based on patient characteristics and judgment of operating surgeon (i.e., with those requiring greater intraocular pressure control receiving three versus two iStents); potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice). Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias in measurement of outcomes: CDVA measured by Snellen, which is not considered reliable, valid, or discriminative.[96] Bias in selection of the reported result: CDVA only reported for 12-month follow-up time point.

[bb] Serious indirectness.[83] CDVA measured by Snellen, which is not considered reliable, valid, or discriminative.[96]

[cc] Serious imprecision.[83] Only one study and no measures of variability.

[dd] One retrospective cohort study.[82]

[ee] Serious risk of bias.[82] Bias due to confounding: participants in the different treatment arms were systematically different; Trabeculectomy + Phaco patients had healthy conjunctiva, ECP + Phaco patients had thin conjunctiva or plateau iris; potential confounding variables not controlled for in the analysis. Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias due to missing data: substantial amount of missing data, amount of missing data not balanced across groups, and reasons for missing data not reported. Bias in measurement of outcomes: VA measured by or Snellen converted to logMAR for analysis, which is not considered reliable, valid, or discriminative.[96]

[ff] Serious indirectness.[82] VA measured by or Snellen converted to logMAR for analysis, which is not considered reliable, valid, or discriminative.[96]

[gg] Serious imprecision.[82] Only a single study and the variability in the estimate (standard deviation) was similar in magnitude to the parameter (mean).

GRADE Table for Research Question 4

Table 43: Adverse Events and Harms of MIGS + Cataract Surgery Versus Comparators in Adults With Glaucoma

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: ECP + Phaco Vs. Phaco Alone											
4	Prospective cohort and retrospective cohort[a]	Very serious risk of bias[b]	No serious inconsistency	Serious indirectness[c]	Serious imprecision[d]	None	472	224	**Mixed Findings; ECP + Phaco [<]/</[=] Phaco Alone:** **Adverse events:** • ECP + Phaco < Phaco[73] • ECP + Phaco [<] Phaco[72,75] • ECP + Phaco [=] Phaco[84] Across studies, adverse events were minor in all treatment groups except for the following major complications that occurred only in the ECP + Phaco groups: • Intracameral tissue plasminogen activator injection with synechiolysis, n = 1[72] • Retinal detachment, n = 3[73,75] • Requirement for penetrating keratoplasty, n = 1[75]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: iStents + Phaco Vs. Phaco Alone											
2	RCTs[e]	Very serious risk of bias[f]	No serious inconsistency	Serious indirectness[g]	Serious imprecision[h]	None	129	147	**iStent + Phaco [=] Phaco Alone:** **Adverse events:** • All minor; iStent + Phaco [=] Phaco[34,66-68] **Secondary surgery required:** • iStent + Phaco (4.3%) [=] Phaco (5.1%)[34,68]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: 2 iStents + Phaco Vs. Phaco Alone											
1	RCT[i]	Very serious risk of bias[j]	No serious inconsistency	Serious indirectness[k]	Serious imprecision[l]	None	17	16	**2 iStents + Phaco [<] Phaco Alone:** **Adverse events:** • All minor; 2x iStent + Phaco [<] Phaco (only complication was iStent malposition; 18%)[69]	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: CyPass Micro-Stent + Phaco Vs. Phaco Alone											
1	RCT[m]	Serious risk of bias[n]	No serious inconsistency	Serious indirectness[o]	Serious imprecision[p]	None	374	131	**Mixed Findings; CyPass Micro-Stent + Phaco =/> Phaco Alone:**[70] **Adverse events:** • CyPass Micro-Stent + Phaco = Phaco • Exception; transient (≤ 30 d) BCVA loss: CyPass Micro-Stent + Phaco (8.8%) > Phaco (15.3%) All minor, except for: • BCVA loss ≥ 10 letters (≥ 2 lines) at 24 mo: 1.1% in CyPass Micro-Stent + Phaco, 0% in Phaco • Visual field loss progression: 6.7% in CyPass Micro-Stent + Phaco; 9.9% in Phaco **Secondary surgery required:** • CyPass Micro-Stent + Phaco (5.5%) = Phaco (5.3%)	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Cataract Surgery Alone: Hydrus Microstent + Phaco Vs. Phaco Alone											
2	RCTs[q]	No serious risk of bias[r]	No serious inconsistency	Serious indirectness[s]	Serious imprecision[t]	None	419	237	**Mixed Findings; Hydrus Microstent + Phaco =/</[?] Phaco alone:** **Adverse events:** In one RCT:[71] • Focal peripheral anterior synechiae (minor) at 1 y follow-up: Hydrus Microstent + Phaco (12.0%) < Phaco alone (2.0%) • Focal peripheral anterior synechiae (minor) at 2 y follow-up: Hydrus Microstent + Phaco (18.8%) < Phaco alone (2.0%) • All other adverse events at 1 and 2 y follow-up: Hydrus Microstent = Phaco All minor except the following (not significantly different between groups; Hydrus Microstent + Phaco and Phaco alone, respectively):	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									• Retinal detachment in year 1: 0.0%, 2.0% • Anterior ischemic optic neuropathy in year 1: 0.0%, 2.0% • BCVA loss > 2 lines in year 1: 0.0%, 6.0% • BCVA loss > 2 lines in year 2: 0.0%, 2.0% In the other RCT:[88] • No statistical comparisons between groups • All minor except for the following (Hydrus Microstent + Phaco and Phaco alone respectively): ○ BCVA loss ≥ 2 lines ≥ 3 mo, 1.4%, 1.6% ○ Worsening of VF mean deviation by 2.5 dB, 4.3%, 5.3% ○ Development of neovascular glaucoma and secondary angle closure, 1%, 0.5% **Secondary glaucoma surgery:** In one RCT:[71] • In year 1: None in either group • In year 2: Hydrus Microstent + Phaco (2.1%) = Phaco alone (4.1%) In the other RCT:[88] • No statistical comparisons between groups; 1.1% and 2.7% in Hydrus Microstent + Phaco and Phaco alone, respectively		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Goniotomy With KDB + Phaco Vs. iStent + Phaco											
1	Retrospective cohort[u]	Serious risk of bias[v]	No serious inconsistency	Serious indirectness[w]	Serious imprecision[x]	None	KDB + Phaco, 237 iStent + Phaco, 198	NA[y]	**Mixed Findings; KDB + Phaco =/> iStent + Phaco:[86]** **Adverse events:** • All minor • IOP spikes: KDB + Phaco (6.3%)	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									> iStent + Phaco (12.6%) • All other adverse events: KDB + Phaco = iStent + Phaco		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Trabectome + Phaco Vs. 2x iStent + Phaco											
2	Retrospective cohort[z]	Serious risk of bias[aa]	No serious inconsistency	Serious indirectness[bb]	Serious imprecision[cc]	None	Trabectome + Phaco, 88 2x iStent + Phaco, 83	NA[y]	**Trabectome + Phaco </= iStent + Phaco:[79]** **Adverse events:** • All minor • Hyphema: Trabectome + Phaco < 2x iStent + Phaco[78] • All other adverse events: Trabectome + Phaco = 2x iStent + Phaco[78] • Trabectome + Phaco < 2x iStent + Phaco[79] **Secondary glaucoma surgery:** • Trabectome + Phaco = 2x iStent + Phaco[78] • Trabectome + Phaco [<] 2x iStent + Phaco[79]	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Trabectome + MICS Vs. 2x iStent Inject + MICS											
1	Retrospective cohort[dd]	Serious risk of bias[ee]	No serious inconsistency	Serious indirectness[ff]	Serious imprecision[gg]	None	Trabectome + MICS, 25 2x iStent Inject + MICS, 25	NA[y]	**Trabectome + MICS [=] 2x iStent Inject + MICS:[77]** **Adverse events:** • All minor • Trabectome + MICS [=] 2x iStent Inject + MICS **Secondary glaucoma surgery:** • Trabectome + MICS [=] 2x iStent Inject + MICS	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: Different Numbers of iStents + Phaco											
2	Retrospective cohort and non-randomized controlled clinical trial[hh]	Serious risk of bias[ii]	No serious inconsistency	Serious indirectness[jj]	Serious imprecision[kk]	None	iStent + Phaco, 39 2x iStent + Phaco, 58 3x iStent + Phaco, 25	NA[y]	**1 iStent + Phaco [<]/[?] 2 iStents + Phaco:** **Adverse events:** • 1 iStent + Phaco [<] 2x iStent + Phaco[80] • All minor except for 1 major complication in the iStent + Phaco group (central retinal vein	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									occlusion leading to development of anterior-chamber neovascularization and neovascular glaucoma) **2 iStents + Phaco [?] 3 iStents + Phaco:** **Adverse events** were not reported separately for each group.[83] All were minor (exception: death due to unrelated systemic illness, 1 patient).		
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: ECP + iStent + Phaco Vs. iStent + Phaco											
1	Retrospective cohort[ll]	Serious risk of bias[mm]	No serious inconsistency	Serious indirectness[nn]	Serious imprecision[oo]	None	ECP + iStent + Phaco, 51 iStent + Phaco, 50	NA[y]	**ECP + iStent + Phaco [=] iStent + Phaco:**[81] **Adverse events:** • All minor • ECP + iStent + Phaco [=] iStent + Phaco **Secondary glaucoma surgery:** • ECP + iStent + Phaco [=] iStent + Phaco	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. A Different MIGS + Cataract Surgery: ECP + Phaco Vs. Trabectome + Phaco											
1	Retrospective cohort[pp]	Serious risk of bias[qq]	No serious inconsistency	Serious indirectness[rr]	Serious imprecision[ss]	None	ECP + Phaco, 35 Trabectome + Phaco, 26	NA[y]	**ECP + Phaco [?] Trabectome + Phaco:**[89] **Adverse events:** All minor; not compared statistically between groups **Secondary glaucoma surgery:** No eyes required secondary surgery in either group	⊕OOO VERY LOW	CRITICAL
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery: Trabectome + Phaco Vs. Trabeculectomy With MMC + Phaco											
1	RCT[tt]	Very serious risk of bias[uu]	No serious inconsistency	Serious indirectness[vv]	Serious imprecision[ww]	None	10	9	**Trabectome + Phaco = Trabeculectomy with MMC + Phaco:**[87] **Early or late post-operative complications:** • Trabectome + Phaco = Trabeculectomy + Phaco • All minor, except hypotony	⊕OOO VERY LOW	CRITICAL

Quality Assessment							Summary of Findings				Importance
							No. of Eyes		Effect	Quality	
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	MIGS	Comparator			
									maculopathy (22% in Trabeculectomy + Phaco group) **Secondary glaucoma surgery:** • Trabectome + Phaco = Trabeculectomy + Phaco		
MIGS + Cataract Surgery Vs. Filtration Surgery + Cataract Surgery: ECP + Phaco Vs. Trabeculectomy With MMC + Phaco											
1	Retrospective cohort[xx]	Serious risk of bias[yy]	No serious inconsistency	Serious indirectness[zz]	Serious imprecision[aaa]	None	24	29	**ECP + Phaco </[?] Trabeculectomy with MMC + Phaco:**[82] **Adverse events:** • All minor • IOP spike: ECP + Phaco < Trabeculectomy + Phaco • Intraoperative complications: ECP + Phaco [<] Trabeculectomy + Phaco • Post-operative complications: ECP + Phaco [>] Trabeculectomy + Phaco	⊕OOO VERY LOW	CRITICAL

= = not significantly different between groups; [=] = not compared statistically but tendency for no difference between groups; > = intervention more favourable than comparator; < = intervention less favourable than comparator; [<] = not compared statistically but tendency for intervention less favourable than comparator; [?] = not compared statistically or non-interpretable; 2x = two devices; 3x = three devices; dB = decibels; ECP = endoscopic cyclophotocoagulation; IOP = intraocular pressure; BCVA = best-corrected visual acuity; d = day; KDB = Kahook Dual Blade; MICS = micro-incision cataract surgery; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = months; NA = not applicable; no. = number; Phaco = phacoemulsification; RCT = randomized controlled trial; VF = visual field; vs. = versus; wk = weeks; y = years.

Note: Data were collected by RCT, non-randomized controlled clinical trial, retrospective or prospective cohort, with up to 4 years of follow-up. The method of measuring adverse events or harms was not reported in any study. The CyPass Micro-Stent was voluntarily withdrawn from the global market by the manufacturer in August 2018 due to five-year data from a long-term safety study;[37,38] however, at the time of report publication, this device was still active in the MDALL and is therefore included in this report.

[a] One prospective cohort study[84] and three retrospective cohort studies.[72,73,75]

[b] Very serious risk of bias. Bias due to confounding: retrospective study and rationale for assigning treatments likely to be different between groups;[72,73,75] baseline characteristics not reported for Phaco alone group so unable to assess whether groups were systematically different at baseline;[72] treatment assignment based on patient characteristics and groups were systematically different;[73] baseline characteristics were different between groups;[73,84] treatment group was assigned based on patient choice and treatment availability;[75] how participants were prospectively assigned to groups was not reported;[84] potential confounding variables not controlled for in analyses.[72,73,75,84] Bias in selection of participants: only those with complete data or sufficient follow-up were included and it is possible that those with complete data or a given follow-up duration were systematically different from those without complete data or a particular follow-up duration (i.e., different from those in routine clinical practice).[72,73,84] Bias due to deviations from intended interventions: important co-intervention may not have been balanced between groups (number of medications was not reported in one group;[72] absolute number of medications not compared statistically between groups[73]); important co-intervention not balanced between groups (number of medications significantly different between groups).[75,84] Bias due to missing data: reasons for patient exclusion only reported for the ECP + Phaco group;[72] low risk up to 24 months of follow-up but large amount of missing data at later time points and reasons not reported.[84] Bias in measurement of outcomes: method of measuring adverse events and harms not specified.[72,73,75,84] Bias in selection of the reported result: statistical comparisons not conducted or reported.[72,75,84]

[c] Serious indirectness.[72,73,75,84] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[d] Serious imprecision.[72,73,75,84] Relatively few adverse events or harms reported and unclear method of measurement, and no measures of variability.

[e] Two RCTs in four publications.[34,66-68]

[f] Very serious risk of bias. Selection bias: no indication of allocation concealment.[34,66-68] Detection bias: method of measuring adverse events and harms not specified.[34,66-68] Attrition bias: low-risk up to 15 months of follow-up (reasons for missing data reported and not likely to be related to the outcome), but large amount of missing data at four-year follow-up and amount not balanced across groups;[66,67] large amount of missing data and reasons for missing data may be related to the true outcome (e.g., those with failed Phaco due to adverse event were excluded post-randomization).[34,68] Reporting bias: statistical comparisons not conducted or reported.[34,66-68]

[g] Serious indirectness.[34,66-68] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[h] Serious imprecision.[34,66-68] Relatively few measures of adverse events or harms, and no measures of variability.

[i] One RCT.[69]

[j] Very serious risk of bias.[69] Selection bias: no indication of allocation concealment. Detection bias: method of measuring adverse events and harms not specified. Reporting bias: statistical comparisons not conducted or reported.

[k] Serious indirectness.[69] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[l] Serious imprecision.[69] Relatively few measures of adverse events or harms, and no measures of variability.

[m] One RCT.[70]

[n] Serious risk of bias.[70] Selection bias: no indication of allocation concealment. Detection bias: method of measuring adverse events and harms not specified.

[o] Serious indirectness.[70] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[p] Serious imprecision.[70] Only a single study; relatively few adverse events or harms and no measures of variability.[70]

[q] Two RCTs.[71,88]

[r] Serious risk of bias.[71,88] Possible risk of selection bias; concealment not explicitly specified but likely, based on method of randomization (online computer algorithms). Detection bias: method of measuring adverse events and harms not specified.

[s] Serious indirectness.[71,88] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[t] Serious imprecision.[71,88]No measures of variability.

[u] One retrospective cohort study.[86]

[v] Serious risk of bias.[86] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups; significant differences between groups at baseline; potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with six-month complete data were included and it is possible that those with complete data were systematically different from those without complete data (i.e., different from those in routine clinical practice). Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias due to missing data: large amount of missing data at one month and three months, reasons for missing data not reported, and amount of missing data not balanced across groups. Bias in measurement of outcomes: method of measuring adverse events and harms not specified.

[w] Serious indirectness.[86] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[x] Serious imprecision.[86] Only a single study; relatively few adverse events or harms and no measures of variability.

[y] In these studies, one MIGS performed in combination with cataract surgery was compared with another MIGS combined with cataract surgery.[77-81,83,86]

[z] Two retrospective cohort studies.[78,79]

[aa] Serious risk of bias. Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups;[78,79] different surgeons performed procedures in the different treatment arms;[79] potential confounding variables not controlled for in analyses.[78,79] Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice).[78,79] Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups).[78] Bias due to missing data: substantial amount of missing data, amount of missing data not balanced across groups and analyses conducted with last observation carried forward (but

disease progression or treatment effectiveness may change over time).[78] Bias in measurement of outcomes: method of measuring adverse events and harms not specified.[78,79] Bias in selection of the reported result: different numerical values reported in the abstract and text, leading to unclear interpretation of findings.[79]

[bb] Serious indirectness.[78,79] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[cc] Serious imprecision.[78,79] No measures of variability.

[dd] One retrospective cohort study.[77]

[ee] Serious risk of bias.[77] Bias in selection of participants: only those with complete follow-up were included and it is possible that those with versus without complete follow-up were systematically different (i.e., different from those in routine clinical practice). Bias due to deviations from intended interventions: by design the post-operative medication regimen was different between groups and the number of medications was significantly different between groups at six-week follow-up. Bias in measurement of outcomes: method of measuring adverse events and harms not specified. Bias in selection of the reported result: statistical comparisons not conducted or reported.

[ff] Serious indirectness.[77] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[gg] Serious imprecision.[77] Only a single study; relative few adverse events or harms and no measures of variability.

[hh] One retrospective cohort[80] and one non-randomized controlled clinical trial.[83]

[ii] Serious risk of bias. Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups;[80] treatment assigned based on patient characteristics and judgment of operating surgeon (i.e., with those requiring greater IOP control receiving three versus two iStents);[83] potential confounding variables not controlled for in analyses.[80,83] Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice).[83] Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups).[83] Bias due to missing data: substantial loss to follow-up, amount of missing data not balanced across groups, and reasons for missing data not reported.[80] Bias in measurement of outcomes: method of measuring adverse events and harms not specified.[80,83] Bias in selection of the reported result: statistical comparisons not conducted or reported;[80] results for adverse events and harms not reported separately for each group.[83]

[jj] Serious indirectness.[80,83] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[kk] Serious imprecision.[80,83] Relatively few adverse events or harms and no measures of variability;[80,83] adverse events not reported separately for each group.[83]

[ll] One retrospective cohort study.[81]

[mm] Serious risk of bias.[81] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups, groups not matched on baseline characteristics, and potential confounding variables not controlled for in analyses. Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias in measurement of outcomes: method of measuring adverse events and harms not specified. Bias in selection of the reported result: statistical comparisons not conducted or reported; specific values not reported for the iStent + Phaco group.

[nn] Serious indirectness.[81] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[oo] Serious imprecision.[81] Only a single study; relatively few adverse events or harms and no measures of variability.

[pp] One retrospective cohort study.[89]

[qq] Serious risk of bias.[89] Bias due to confounding: retrospective design and rationale for assigning treatments likely to be different between groups; some baseline characteristics (e.g., age) different between groups; potential confounding variables not controlled for in analyses. Bias in selection of participants: only those with 12-month follow-up were included and it is possible that those with 12-month follow-up were systematically different from those with shorter follow-up (i.e., different from those in routine clinical practice); at least one patient who did not meet inclusion criteria was included (the inclusion criteria specified age > 40 years, but the range of ages in one group was reported as 30 to 85 years). Bias in selection of the reported result: statistical comparisons not conducted or reported.

[rr] Serious indirectness.[89] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[ss] Serious imprecision.[89] Only a single study; no measures of variability.

[tt] One RCT.[87]

[uu] Very serious risk of bias.[87] Selection bias: inclusion criteria were altered after the start of the study due to slow patient recruitment and specific changes to inclusion criteria were not reported. Performance bias: the study occurred over a long duration and how the intervention (Trabectome + Phaco) was conducted changed over the course of the study (i.e., length of the ablation cleft increased from ~90 to 160 degrees). Detection bias: method of measuring adverse events and harms not specified. Attrition bias: only one patient missing data in each group but the sample size was so small that this still represented a substantial proportion of the data (~10% per group). Other bias: the trial was stopped early due to difficulties in patient recruitment and lack of clinical equipoise over time, so fewer participants were recruited than planned a priori.

[vv] Serious indirectness.[87] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[ww] Serious imprecision.[87] Only a single study; relatively few adverse events or harms and no measures of variability.[xx] One retrospective cohort study.[82]

[yy] Serious risk of bias.[82] Bias due to confounding: participants in the different treatment arms were systematically different; Trabeculectomy + Phaco patients had healthy conjunctiva, ECP + Phaco patients had thin conjunctiva or plateau iris; potential confounding variables not controlled for in the analysis. Bias due to deviations from intended interventions: important co-intervention not balanced between groups (number of medications significantly different between groups). Bias due to missing data: substantial amount of missing data, amount of missing data not balanced across groups, and reasons for missing data not reported. Bias in measurement of outcomes method of measuring adverse events and harms not specified. Bias in selection of the reported result: some statistical comparisons not conducted or reported.

[zz] Serious indirectness.[82] Method of measuring adverse events or harms was not specified; therefore, it is unclear whether direct or surrogate measures were used or whether data on all patient-important adverse events or harms were collected.

[aaa] Serious imprecision.[82] Only a single study; relatively few adverse events or harms and no measures of variability.

Appendix 14: Additional Meta-Analysis of Clinical Data for the Economic Evaluations

Rationale

The purpose of this meta-analysis was to support the economic analysis by providing the estimates of the clinical effectiveness of Hydrus Microstent + Phacoemulsification (Hydrus + Phaco), compared with Phaco alone 12 months after surgery. In the economic model, relative treatment efficacy was described by the annual reduction in intraocular pressure that was consequently mapped to change in visual field to project the annual rate of change in glaucoma progression by treatment.

Methods

The outcome of interest was washed-out diurnal intraocular pressure (DIOP). The mean values of washed-out DIOP were extracted directly from Pfeiffer et al.[71] However, Samuelson et al. did not report the mean values and standard deviations (SDs) for the results at month 12.[88] The mean values at month 12 were therefore estimated based on the mean values at baseline and the reduction in DIOP at month 12.[88] The SDs of the estimates were derived from the 24-month results because the 12-month SDs tended to be smaller than 24-month SDs in most publications (e.g., results in Pfeiffer 2015). This imputation might lead to more conservative overall estimates (i.e., less likely to show statistical significance between groups).

In brief, a random-effects meta-analysis was conducted using R (version 3.4.2) [213] and RStudio (version 1.0.143)[214] to estimate the mean differences in clinical effectiveness between groups and corresponding 95% confidence intervals. A forest plot was created for individual summary estimates. The risk of publication bias was assessed using a funnel plot.

Results

There were two randomized controlled trials included for the meta-analysis of the clinical effectiveness of Hydrus + Phaco compared with Phaco alone at 12 months after surgery.[71,88]

The risk of publication bias was minimal as shown in Figure 27.

The between-study variance, tau squared, was zero based on a random-effects model and a restricted maximum-likelihood method. The heterogeneity test showed Q = 0.32 (P = 0.57) and, the I^2 statistic was zero; both tests suggest minimal statistical heterogeneity between the two trials.

Figure 27: The Funnel Plot of the Comparison of Washed-Out Diurnal Intraocular Pressure Between Hydrus + Phaco and Phaco Alone

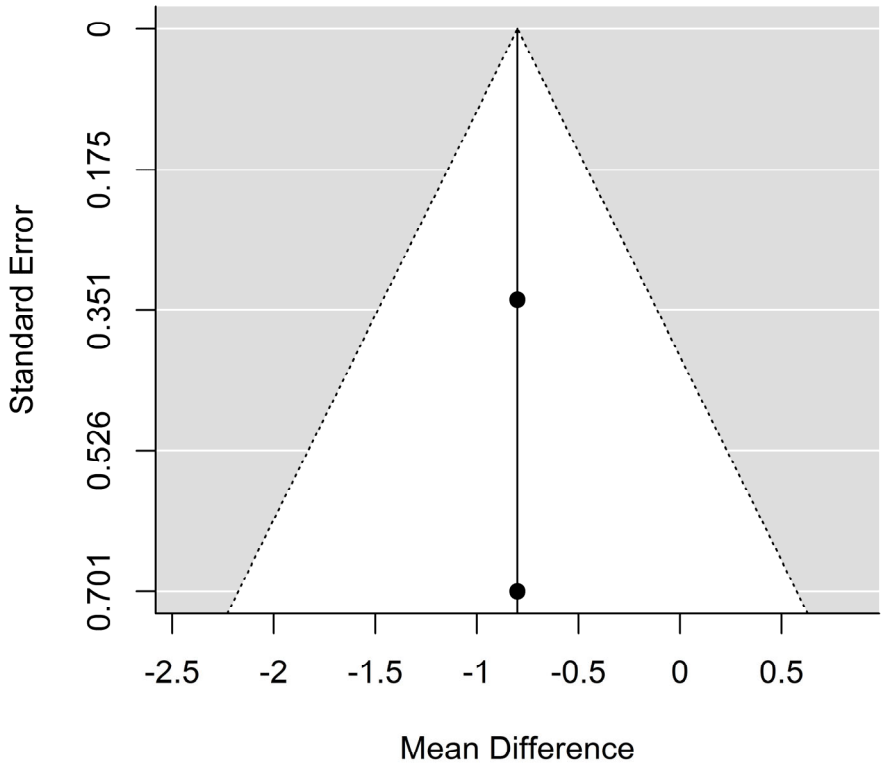
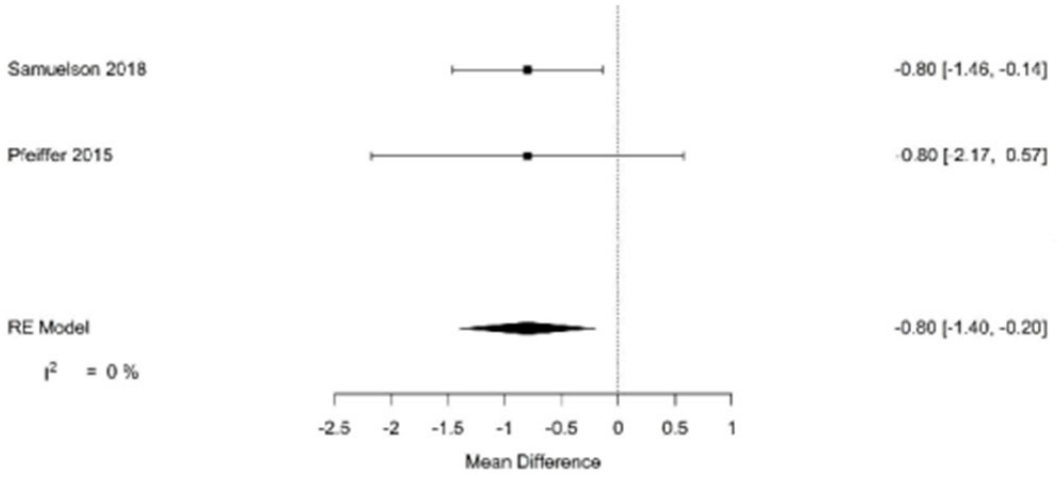


Figure 28: Mean difference [95% Confidence Interval] in Washed-Out DIOP Between Hydrus + Phaco and Phaco Alone Groups at 12-Month Follow-Up



Appendix 15: Detailed Economic Model Inputs

Table 44: Detailed Clinical Outcomes From the Clinical Review

Model	Comparison	Baseline VF (dB)	IOP reduction at 12 months (mm Hg)	Medication reduction at 12 months	Reference
Model 1: MIGS vs. Pharmacotherapy	1. 2x iStent vs. Travoprost 2. 2x iStent Inject vs. Latanoprost + Timolol	1. –7.5 vs. –5.8 2. NR	1. 11.8 vs. 11.2 (*P* = NR) 2. 12.2 vs. 11.6 (*P* = NR)	NA NA	1. Vold et al. 2016[58] 2. Fea et al. 2014[36]
Model 2: MIGS vs. laser therapy	Hydrus Microstent vs. SLT	–8.43 vs –3.04	6.6 vs. 7.3 (*P* = 0.57)	1.4 vs. 0.5 (*P* < 0.01)	Fea et al. 2017[62]
Model 3: MIGS vs. filtration surgery	1. Model 3b: ECP vs. glaucoma drainage device (BGI or AGI) 2. Model 3a: Trabectome vs. Trabeculectomy with MMC 3. 2x iStent Inject vs. Trabeculectomy with MMC 4. Trabectome or 2x iStent Inject vs. Trabeculectomy with MMC 5. Xen45 with MMC vs. Trabeculectomy with MMC[65]	1. –13.94 vs. –17.33 2. NR 3. NR 4. NR 5. –6.9 vs. –6.0	1. 7.8 vs. 9.3 (*P* = NR); (24 mo) 14.07 vs. 14.73 (*P* = 0.7) 2. 10.7 vs. 14.1 (*P* < 0.01); (6 mo) 4.4 vs. 15.1 (*P* = NR) 3. (6 mo) 5.3 vs. 15.1 (*P* = NR) 4. (6 mo) 5.7 vs. 15.1 (*P* = NR) 5. 11 vs. 11 (*P* = 0.98)	1. 1.6 vs. 1.5 (*P* = 0.74); (24 mo) 1 vs. 1 (*P* = NR) 2. 1.5 vs. 2.7 (*P* = NR); (6 mo) 0.28 vs. 1.82 3. (6 mo) inc. 0.05 vs. 1.82 4. (6 mo) 0.69 vs. 1.82 5. NR	1. Murakami et al. 2017;[63] Lima et al. 2004[61] 2. Jea et al. 2012;[64] Pahlitzsch et al. 2017[25] 3. Pahlitzsch et al. 2017[25] 4. Pahlitzsch et al. 2017[25] 5. Schlenker et al. 2017[65]
Model 4: MIGS + cataract surgery vs. cataract surgery alone	1. ECP + Phaco vs. Phaco alone 2. iStent + Phaco vs. Phaco alone 3. 2x iStent + Phaco vs. Phaco alone 4. CyPass Micro-Stent + Phaco vs. Phaco alone 5. Hydrus Microstent + Phaco vs. Phaco alone	1. –13.36 vs. –4.74 –17.01 vs. NR 2. –3.75 vs. –3.74 3. NR 4. –3.37 vs. –3.77 5. –5.6 vs. –8.4 –3.61 vs. –3.61	1. 6.0 vs. NR 4.5 vs. 1.8 3.2 vs. 2.0 2.5 vs. 1.5 2.1 vs. 0.6 2. Meta-analysis: –0.42 (–1.30 to 0.46) (6 mo) 1.6 vs. 2.4 3. (6 mo) 3.2 vs. 2.4 6.6 vs. 3.8 4. 7.9 vs. 6.2 5. 9.7 vs. 9.2 8.5 vs. 6.3 (*P* < 0.01) Meta-analysis: –0.8 (–1.4, –0.2) (*P* < 0.01)	1. 0.8 vs. NR 0.73 vs. 0.23 0.49 vs. 0.02 1.1 vs. 0.1 1.1 vs. 0.6 2. Meta-analysis: –0.25 (–0.52 to 0.01) (6 mo) 0.8 vs. 0.3 3. (6 mo) 1.1 vs. 0.3 1.1 vs. 0.5 4. 1.2 vs. 0.6 5. (24 mo) 1.5 vs. 1.0 (24 mo) 1.4 vs. 1.0 Meta-analysis: (24 mo) –0.41 (–0.56, –0.27) (*P* < 0.01)	1. Kang et al. 2017;[72] Perez Bartolome et al. 2017;[73] Sheybani et al. 2015;[74] Siegel et al. 2015;[75] Francis et al. 2014[84] 2. Meta-analysis: Fea et al. 2015;[66] Craven et al. 2012;[68] El Wardani et al. 2015[76] 3. El Wardani et al. 2015;[76] Fernandez-Barrientos et al. 2010[69] 4. Vold et al. 2016[70] 5. Pfeiffer et al. 2015;[71] Samuelson et al. 2018[88]

Model	Comparison	Baseline VF (dB)	IOP reduction at 12 months (mm Hg)	Medication reduction at 12 months	Reference
Model 5: MIGS + cataract surgery vs. filtration surgery + cataract surgery	1. Trabectome + Phaco vs. Trabeculotomy + Phaco 2. ECP + Phaco vs. Trabeculectomy with MMC + Phaco	1. –11.6 vs. –15.38 NR 2. NR	1. 5.4 vs. 7.7 (P = 0.53) 2.7 vs. 6.4 (P = 0.35) 2. (6 mo) 5.7 vs. 6.2 (P = 0.376)	1. 1.0 vs. 1.6 (P = 0.027) 1.3 vs 0.65 (P = 0.41) 2. (6 mo) 1.17 vs. 2.1 (P < 0.05)	1. Kinoshita-Nakano et al. 2018;[85] Ting et al. 2018[87] 2. Marco et al. 2017[82]

2X = two devices; AGI = Ahmed glaucoma implant; dB = decibels; BGI = Baeveldt glaucoma implant; ECP = endoscopic cyclophotcoagulation; inc = incremental; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; MMC = mitomycin C; mo = month; NA = not applicable; NR = not reported; Phaco = phacoemulsification; SLT = selective laser trabeculoplasty; VF = visual field; vs. = versus.

Note: Red font highlights the clinical data informing the reference-case analysis.

Table 45: Detailed Adverse Events

	Major Complications	Minor Complications	Secondary Surgical Interventions	Reference
Model 1: MIGS Vs. Pharmacotherapy				
iStent Inject[a]	NA	Hyphema (2%); progression of cataract (20%) Total: 22%	NA	Vold et al. 2016[58]
Pharmacotherapy	NA	Progression of cataract (17%) Total: 17%	NA	Vold et al. 2016[58]
Model 2: MIGS Vs. Laser Therapy				
Hydrus Microstent	Corneal edema (9.7%) Total: 10%	IOP spike (6.45%); temporary decrease in VA > 2 lines lasting < 7 d (9.68%) Total: 16%	NA	Fea et al. 2017[62]
Laser Therapy (SLT)	NA	SLT: Eye discomfort (40%) Total: 40%	NA	Fea et al. 2017[62]
Model 3: MIGS Vs. Filtration Surgery				
ECP	Failure of the corneal graft (2.94%); retinal detachment (2.94%); hypotony (2.94%); phthisis bulbi (2.94%) Total: 12%	Choroid detachment (2.94%); hyphema (17.64%); inflammatory precipitates in anterior chamber (11.76%) Total: 32%	NA	Lima et al. 2004[61]
AGI (GDD-2)	Failure of the corneal graft (11.76%); retinal detachment (5.88%); tube exposure (5.88%); endophthalmitis (2.94%) Total: 26%	Choroid detachment (17.64%); shallow anterior chamber (17.64%); hyphema (14.7%); cystic bleb (14.7%); tube block (5.88%); corneal touch (5.88%) Total: 76%	NA	Lima et al. 2004[61]
Trabectome	NA	Early IOP spike (3.5%) Total: 4%	NA	Jea et al. 2012[64]
Xen45	Malignant glaucoma (2.2%) Total: 2%	Anterior-chamber reformation (12%) Total: 12%	Needling (43.2%); anterior-chamber reformation (11.9%) Total: 55%	Schlenker et al. 2017[65]
Trabeculectomy	Jea: Persistent hypotony (4.9%); shallow anterior chamber (7.8%) Total: 13%	Jea: Early hypotony (9.8%); wound leak (11.8%); Choroidals (3.9%); early IOP spike (2.9%); hyphema (2.9%); cystoid macular edema (2.0%); conjunctival and tenon buttonhole (2.9%)	Jea: NA	Jea et al. 2012;[64] Schlenker et al. 2017[65]

	Major Complications	Minor Complications	Secondary Surgical Interventions	Reference
	Schlenker: NA	Total: 36% Schlenker: Leak/dehiscence (7.1%); laser suture lysis (49.7%) Total: 57%	Schlenker: Needling (30.8%); anterior-chamber reformation (7.7%); bleb repair/conjunctival suturing (5.9%); iris sweep/synechiolysis (2.4%) Total: 47%	
Model 4: MIGS + Phaco Vs. Phaco				
ECP + Phaco	NA	Kang: Uveitis (6.45%) Total: 7% Perez: Raised IOP (7.24%); persistent (≥ 6 wk) post-operative uveitis (8.69%); macular edema (5.79%); Total: 22% Francis: Anterior-chamber hemorrhage (2.5%) Total: 3%	Kang: YAG laser (1.6%) Total: 2% Perez: NA Siegel: Secondary procedures (CME development; retinal detachments; penetrating keratoplasty) (2.7%) Total: 3%	Kang et al. 2017;[72] Perez Bartolome et al. 2017;[73] Siegel et al. 2015;[75] Francis et al. 2014[84]
iStent + Phaco	NA	Fea: Stent malposition (16.6%) Total: 17% Craven: Vitreous removal/vitrectomy (4.3%); iris touch (7.0%); stent obstruction (4%); posterior capsular opacification (3%); stent malposition (3%); subconjunctival hemorrhage: (2%); elevated IOP (2%); epiretinal membrane (2%); Iris atrophy (2%) Total: 29% Fernadez-Barrientos: Malpositioned stent (18%) Total: 18%	Craven: Paracentesis (28%); YAG laser capsulotomy (4%); stent repositioning (3%); stent obstruction or replacement (2%) Total: 37%	Fea 2010;[67] Craven et al. 2012;[68] Fernandez-Barrientos et al. 2010[69]
CyPass Micro-Stent + Phaco	Iritis (8.6%) Total: 9%	BCVA loss ≥ 10 letters (≥ 2 lines) of ≤ 30-day duration (8.8%); corneal edema (3.5%); hyphema, transient intraoperative (2.7%); hypotony (IOP < 6 mm Hg) (2.9%); IOP ≥ 10 mm Hg over baseline (4.3%); stent obstruction (2.1%) Total: 24%	Secondary ocular surgical intervention (5.5%) Total: 6%	Vold et al. 2016[70]

	Major Complications	Minor Complications	Secondary Surgical Interventions	Reference
Hydrus Microstent + Phaco	Pfeiffer: Focal peripheral anterior synechiae (19%) Total: 19% Samuelson: NA	Pfeiffer: IOP spike (4%); macular edema (2%); focal peripheral anterior synechiae (12%) Total: 18% Samuelson: Uveitis/iritis requiring steroids (5.6%); conjunctivitis (5.7%); device obstruction/focal peripheral anterior synechiae, nonobstructive (14.9%); device obstruction/focal Peripheral anterior synechiae, obstructive (3.8%); cystoid macular edema (2.2%); subconjunctival hemorrhage (2.4%) Total: 35%	NA Samuelson: Surgical re-intervention in study eye (2.4%) Total: 2%	Pfeiffer et al. 2015;[71] Samuelson et al. 2018[88]
Phaco	Perez/Francis/Fea/Siegel: NA Craven: Iritis (5%) Total: 5% Vold: Iritis (3.8%) Total: 4%	Siegel: NA Perez: Raised IOP (3.33%); persistent (≥ 6 wk) post-operative uveitis (3.33%); macular edema (3.33%) Total: 10% Francis: Significant inflammation (2.5%); CME (3.8%) Total: 6% Fea: Ruptured capsule (4.2%); Total: 4% Craven: Vitreous removal/vitrectomy (2.6%); posterior capsular opacification (7%); subconjunctival hemorrhage (2%); blurry vision (5%); dry eye (2%); elevated IOP (2%); macular edema (2%); foreign body sensation (2%); allergic conjunctivitis (2%); mild pain (2%); rebound inflammation from tapering steroids (2%) Total: 31% Vold: BCVA loss ≥ 10 letters (≥ 2 lines) of ≤ 30-day duration (15.3%); conjunctivitis (2.3%); IOP ≥ 10 mm Hg over baseline (2.3%) Total: 20%	Siegel: CME development (7.7%) Perez/Francis/Fea: NA Craven: Paracentesis (27%); YAG laser capsulotomy (6%); punctal cautery/punctual plugs (2%); trabeculoplasty (2%) Total: 37% Vold: Secondary ocular surgical intervention (5.3%) Total: 5%	Craven et al. 2012;[68] Fea et al. 2010[67] Siegel et al. 2015;[75] Perez Bartolome et al. 2017;[73] Vold et al. 2016;[70] Pfeiffer et al. 2015;[71] Samuelson et al. 2018[88]

	Major Complications	Minor Complications	Secondary Surgical Interventions	Reference
	Pfeiffer: Retinal detachment: (2%) Total: 2% Samuelson: 0%	Pfeiffer: BCVA loss > 2 lines (6%); IOP spike (4%); macular edema (4%); epiretinal membrane (4%) Total: 18% Samuelson: Uveitis/iritis requiring steroids (3.7%); conjunctivitis (7.0%); elevated IOP ≥ 10 mm Hg over baseline (2.7%); device obstruction/focal peripheral anterior synechiae, nonobstructive (2.1%); cystoid macular edema (2.1%) Total: 18%	Pfeiffer: 0% Samuelson: Surgical re-intervention in study eye (4.8%) Total: 5%	
Model 5: MIGS + Phaco Vs. Filtration Surgery + Phaco				
Trabectome + Phaco	NA	Ting: Peripheral anterior synechiae (50%); day 1 IOP spike (50%); hyphema (40%); hypotony (10%); steroid response (10%) Total: 100%	NA	Ting et al. 2018[87]
ECP + Phaco	NA	NA	Vitrectomy (8.3%)	Marco et al. 2017[82]
Trabeculectomy + Phaco	Ting: Hypotony maculopathy (22%); Choroidal effusion (22%) Total: 44% Marco: Choroidal effusion (3.4%); hypotony (17%) Total: 20%	Ting: Peripheral anterior synechiae (11%); say 1 IOP spike (33%); bleb leak (22%); hypotony (33%) Total: 99% Marco: Hypotony (17.2%); laser suture lysis (44.8%); bleb leak (3.4%); bandage contact lens (10.3%) Total: 76%	Ting: NA Marco: Needling of bleb (6.9%) Total: 7%	Ting et al. 2018;[87] Marco et al. 2017[82]

AGI = Ahmed glaucoma implant; BCVA = best-corrected visual acuity; CME = cystoid macular edema; d = day; ECP = endoscopic cyclophotcoagulation; GDD-2 = second Baerveldt glaucoma implant 250 or 350; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; NA = not applicable; Phaco = phacoemulsification; SLT = selective laser trabeculoplasty; VA = visual acuity; YAG = yttrium-aluminum-garnet; vs. = versus; wk = week.

[a] Assumed rate of complications for iStent Inject would be similar to iStent.

Medication Costs

The cost of medications was calculated based on the unit costs from provincial formularies with 21% wastage proposed by Iordanous et al.,[19] and weighted by the proportion of patients in each drug class over total prescriptions.[215] Markup (8% and $8.83 dispensing fees) was included in the sensitivity analysis.

Table 46: Drug Unit Costs (2018 Dollars)

Drug Class/Name	Ontario (Cost per Bottle)	Alberta (Cost per Bottle)
Combination drugs		
Dorzolamide HCL-timolol 0.5% 10 mL	20.95	19.89
Brimonidine-timolol 0.2% 10 mL	44.53	43.36
Latanoprost-timolol 2.5 mL	11.07	11.07
Travoprost-timolol 0.004% 5 mL	58.95	58.95
Average cost per bottle	33.88	33.32
Average annual cost without markup	194.19	192.27
Average annual cost with markup (8% markup and $8.83 per bottle)	271.98	269.90
Carbonic anhydrase inhibitors		
Dorzolamide HCL 2% 5 mL	15.35	15.81
Brinzolamide 1% 5 mL	17.78	17.41
Average cost per bottle	16.57	16.61
Average annual cost without markup	174.86	175.24
Average annual cost with markup (8% markup and $8.83 per bottle)	265.76	266.17
Alpha-agonists		
Brimonidine 0.15% 5 mL	8.66	5.78[a]
Average annual cost without markup	72.53	48.36
Average annual cost with markup (8% markup and $8.83 per bottle)	139.44	113.33
Prostaglandin analogues		
Travoprost 0.004% 5 mL	20.13	20.13
Latanoprost 0.005% 2.5 mL	9.58	9.08
Bimatoprost 0.01% 5 mL	59.3	45.97
Average cost per bottle	29.67	25.06
Average annual cost without markup		
Average annual cost with markup (8% markup and $8.83 per bottle)	89.65 127.72	76.45 113.47
Beta-blockers		
Timolol 0.5% 5 mL	13.65	6.07
Timoptic-XE 0.5% 5 mL	13.65	25.16
Levobunolol 0.5% 5 mL	18.00	17.34
Average cost per bottle	15.10	16.18
Average annual cost without markup	105.68	116.08
Average annual cost with markup (8% markup and $8.83 per bottle)	164.11	175.35
Pilocarpine		
Pilocarpine 2% 5 mL	1.39	1.34
Average annual cost without markup	19.69	18.94
Average annual cost with markup (8% markup and $8.83 per bottle)	124.40	123.59

[a] 0.15% is not a benefit in Alberta, 0.2% was used.

The annual medication costs for Ontario without markup were derived from the following calculations:

One medication:

0.54 * $89.65 + 0.31 * $105.68 + 0.09 * $194.19 + 0.03 * $72.53 + 0.02 * $19.69 = $101

Two medications:

2 * (0.42 * $89.65 + 0.24 * $105.68 + 0.06 * $174.86 + 0.18 * $194.19 + 0.08 * $72.53 + 0.03 * $19.69) = $230

Three medications:
3 * (= 0.31 * $89.65 + 0.15 * $105.68 + 0.12 * $174.86 + 0.12 * $194.19 + 0.24 * $72.53 + 0.07 * $19.69) = $320

Medication costs for Alberta were also derived the same way.

Physician Fees

Physician fees were obtained from Ontario Schedule of Benefit (SOB) and Alberta Medical Association (AMA). Surgery-related fees such as surgeon, anesthetics, surgical assistant, and time costs (assuming 30 mins) were included. Given that not all surgical assistant costs were available in Alberta except for filtration surgery, it was estimated using the units required in Ontario and the time cost in Alberta ($18.29 per 10 mins). For combination procedure in Alberta, fees were reimbursed based on the full amount of the first procedure, and 75% of the lesser procedure.

Table 47: Codes Used for Physician Claims

Procedures	Ontario		Alberta
Trabeculectomy, billing code	E132		26.25B
Surgeon's fee	$550		$970.52
Anesthetics	6 units * $15.01		$219.83
Assistant	0		0
Time cost	$15.01		3 units * $18.29
Total	$655		$1,245
MIGS (proxy code from ON), billing code	More intensive: E132 + E136	Less intensive: E132	26.29A
Surgeon's fee	$550 + $290	$550	$469.05
Anesthetics	$0		$0
Assistant	$0		$0
Time cost	$0		$0
Total	$550 to $840		$469
Laser therapy, billing code	E134		26.34A
Surgeon's fee	$205.55		$416.99
Anesthetics (0 informed by HQO)	$0		$0
Time cost (0 informed by HQO)	$0		$0
Total	$206		$417
Glaucoma filter surgery, billing code	E136 + E132		26.2B
Surgeon's fee	$290 + $550		$1227.58
Anesthetics	6 units * $15.01		$311.45
Assistant	0		$0
Time cost	$15.01		3 units * $18.29
Total	$945		$1,594
Cataract surgery, billing code	E140		27.72A
Surgeon's fee	$397.75		$408.41
Anesthetics (0 informed by HQO)	$0		$0
Time cost (0 informed by HQO)	$0		$0
Total	$398		$408

Procedures	Ontario		Alberta
MIGS + cataract surgery Surgeon's fee	More intensive: E214 + E136 + E950 $729 + $290 + $92.5	Less intensive: E214 + E950 $729 + $92.5	26.29A + 75% of 27.72A $469.05 + 75% * 408.41
Anesthetics Assistant Time cost Total	$0 $0 $0 $822 to $1,112		$219.83 $0 3 units * $18.29 $775
Trabeculectomy + cataract surgery, billing code Surgeon's fee Anesthetics Assistant Time cost Total	E214 + E950 $729 + $92.5 6 units * $15.01 0 $15.01 $927		26.25B + 75% of 27.72A $970.52 + 75% * 408.41 $219.83 $0 3 units * $18.29 $1,552

HQO = Health Quality Ontario; MIGS = minimally invasive glaucoma surgery; ON = Ontario; SA = sensitivity analysis.

Note: Alberta costs excluding assistant costs are included in the sensitivity analysis.

Health State Costs

Physician fees were obtained from the Ontario SOB and the AMA.

Table 48: Codes Used for Health State Costs

Variable Description	Ontario (Billing Code)	Alberta (Billing Code)
Unit Cost Ophthalmologist visit First visit Subsequent visit Optic disc test IOP test VF test Cane Low-vision services (US2006 $511) 2006 US-Can exchange 1.134	 $82.3 (A235) $28.95 (A234) $35 (G820) $40.25 (G432 + 858) $5.1 (G435, $0 in 1st visit) 75% of $31.95 = $24 25% of $693 = $173	 $82.28 (03.03A + CMGP02) $45.74 (03.03A) $46.59 (09.13E + F) $73.57 (09.05A + B) $14.51 (03.12A)[a] $24 $173
Annual Health State Cost Mild stage: 1 visit and 1.5 sets of tests Moderate stage: 2 visits and 2 sets of tests Advanced stage: 3 visits, 2 set of tests + low-vision aid (cane) Severe/blindness: 4 visits, 2 set of tests + low-vision services for 25% patients (US2006 $511)	 82.3 + 1.5 * (35 + 40.25) + 0.5 * 5.1 =198 82.3 + 28.95 + 2 * (35 + 40.25) + 5.1 =267 82.3 + 2 * 28.95 + 2 * (35 + 40.25) + 5.1 = 296 (+24) 82.3 + 3 * 28.95 + 2 * (35 + 40.25) + 5.1 = 325 (+173)	 82.28 + 1.5 * (45.74 + 46.59 + 14.51) = 284 82.28 + 45.74 + 2 * (45.74 + 46.59 + 14.51) =397 82.28 + 2 * 45.74 + 2 * (45.74 + 46.59 + 14.51) = 443 (+24) 82.28 + 3 * 45.74 + 2 * (45.74 + 46.59 + 14.51) = 489 (+173)

IOP = intraocular pressure; VF = visual field.

[a] Original cost is $25.94 add to 75% of base cost (03.03A), so the incremental cost of $14.51 to 100% base cost was used.

Table 49: Values Used for Probabilistic Reference-Case Distributions

Variable Description	Type of Distributions (Values)
Model 1	
Cost of medications (1 to 3 drugs)	Gamma (19.5739, 0.0894)
MIGS OR costs (20% to 80%)	Gamma (105.43, 0.1279)
iStent costs (+/–25%)	Gamma (64, 0.0589)
IOP reduction iStent[a]	Normal (12.2, 2.5)
IOP reduction meds[a]	Normal (11.6, 2.2)
Drug non-adherence (5% to 80%, midpoint: 42.5%)	Beta (425, 575)
Utility moderate	Beta (781, 219)
Utility advanced	Beta (704, 296)
Utility severe	Beta (594, 406)
Utility complications	Beta (101, 899)
Model 2	
MIGS OR costs (20% to 80%)	Gamma (105.43, 0.1279)
Hydrus costs (+/–25%)	Gamma (64, 0.0589)
IOP reduction Hydrus[b]	Normal (6.6, 5.62)
IOP reduction laser[b]	Normal (7.3, 2.53)
Med reduction Hydrus[b]	Normal (1.4, 0.97)
Med reduction laser[b]	Normal (0.5, 1.05)
Utility mild	Beta (847, 153)
Utility moderate	Beta (781, 219)
Utility advanced	Beta (704, 296)
Utility severe	Beta (594, 406)
Utility complications	Beta (101, 899)
Model 3a	
MIGS OR costs (20% to 80%)	Gamma (105.43, 0.1279)
Trabectome costs (+/–25%)	Gamma (64, 0.0841)
IOP baseline MIGS[c]	Normal (28.1, 8.6)
IOP 12-month MIGS[c]	Normal (17.4, 5.9)
IOP baseline surgery[c] (	Normal (26.3, 10.9)
IOP 12-month surgery[c]	Normal (12.2, 5.4)
Med reduction MIGS[c]	Normal (1.5, 1.3)
Med reduction surgery[c]	Normal (2.7, 1.2)
Utility moderate	Beta (781, 219)
Utility advanced	Beta (704, 296)
Utility severe	Beta (594, 406)
Utility complications	Beta (101, 899)
Model 3b	
MIGS OR costs (20% to 80%)	Gamma (105.43, 0.1279)
ECP costs (+/–25%)	Gamma (64, 0.2936)
IOP reduction MIGS[d]	Normal (7.8, 6.5)
IOP reduction surgery[d]	Normal (9.3, 8.3)
Med reduction MIGS[d]	Normal (1.5, 1.3)
Med reduction surgery[d]	Normal (1.6, 1.5)
Utility advanced	Beta (704, 296)
Utility severe	Beta (594, 406)
Utility complications	Beta (101, 899)
Model 4	
MIGS OR costs (20% to 80%)	Gamma (105.43, 0.1279)
Hydrus costs (+/–25%)	Gamma (64, 0.0589)
Relative IOP reduction MIGS (meta-analysis)	Normal (0.8, 0.3046)
IOP reduction Phaco[e]	Normal (6.3, 4.2)
Relative med reduction MIGS (meta-analysis)	Normal (0.4132, 0.0726)
Utility mild	Beta (782, 218)
Utility moderate	Beta (716, 284)

Variable Description	Type of Distributions (Values)
Utility advanced	Beta (639, 361)
Utility severe	Beta (529, 471)
Utility complications	Beta (101, 899)
Model 5	
MIGS OR costs (20% to 80%)	Gamma (105.43, 0.1279)
Trabectome costs (+/–25%)	Gamma (64, 0.0841)
IOP baseline MIGS + Phaco[f]	Normal (21, 5.7)
IOP 12-month MIGS + Phaco[f]	Normal (15.6, 3.5)
IOP baseline surgery + Phaco[f]	Normal (23, 7)
IOP 12-month surgery + Phaco[f]	Normal (15.3, 3.2)
Med reduction MIGS + Phaco[f]	Normal (1, 1.5)
Med reduction surgery + Phaco[f]	Normal (1.6, 1.2)
Utility advanced	Beta (639, 361)
Utility severe	Beta (529, 471)
Utility complications	Beta (101, 899)

ECP = endoscopic cyclophotocoagulation; Hydrus = Hydrus Microstent; IOP = intraocular pressure; med = medication; MIGS = minimally invasive glaucoma surgery; OR = operating room; Phaco = phacoemulsification.

Note: IOP reduction is calculated as 12-month IOP minus baseline IOP, if not specified in the study.

[a] Fea et al. 2014.[36]

[b] Fea et al. 2017.[62]

[c] Jea et al. 2012.[64]

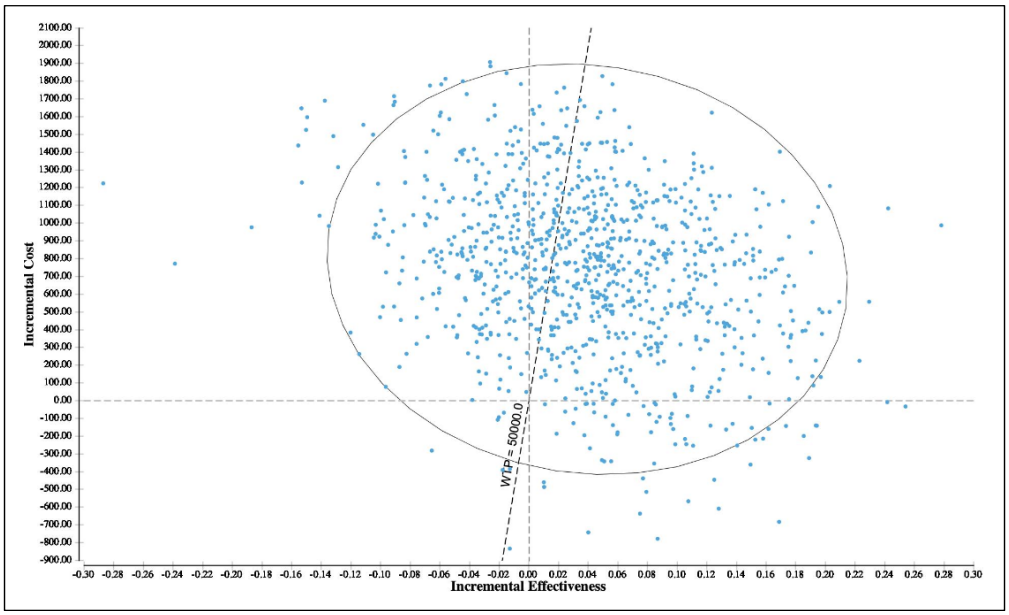
[d] Murakami et al. 2017.[63]

[e] Samuelson et al. 2018.[88]

[f] Kinoshita-Nakano et al. 2018.[85]

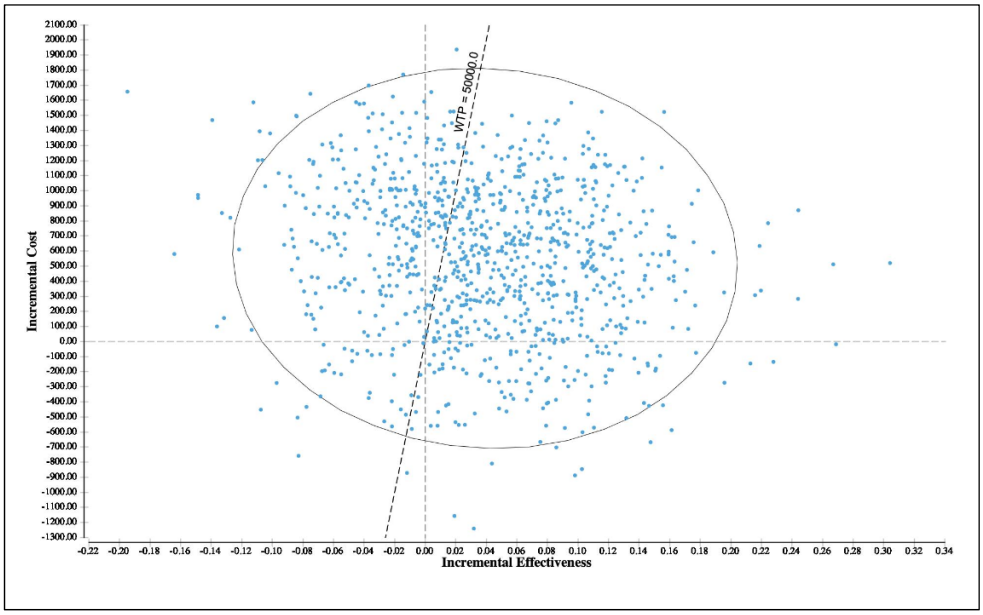
Appendix 16: Incremental Cost-Effectiveness Planes

Figure 29: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 1 — Reference Case (Alberta Perspective)



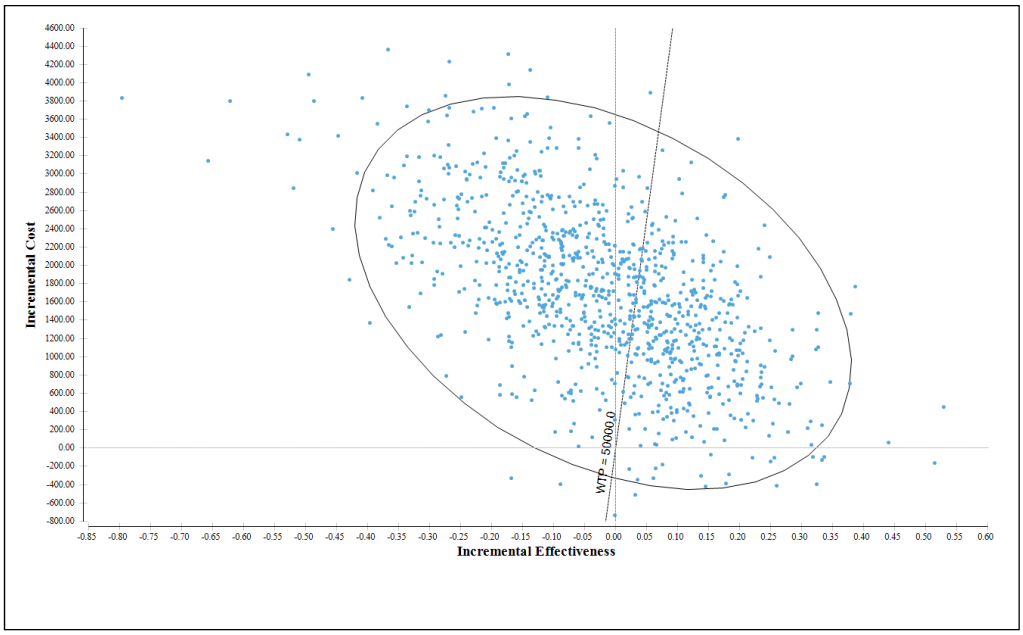
WTP = willingness-to-pay.

Figure 30: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 1 — Ontario Perspective



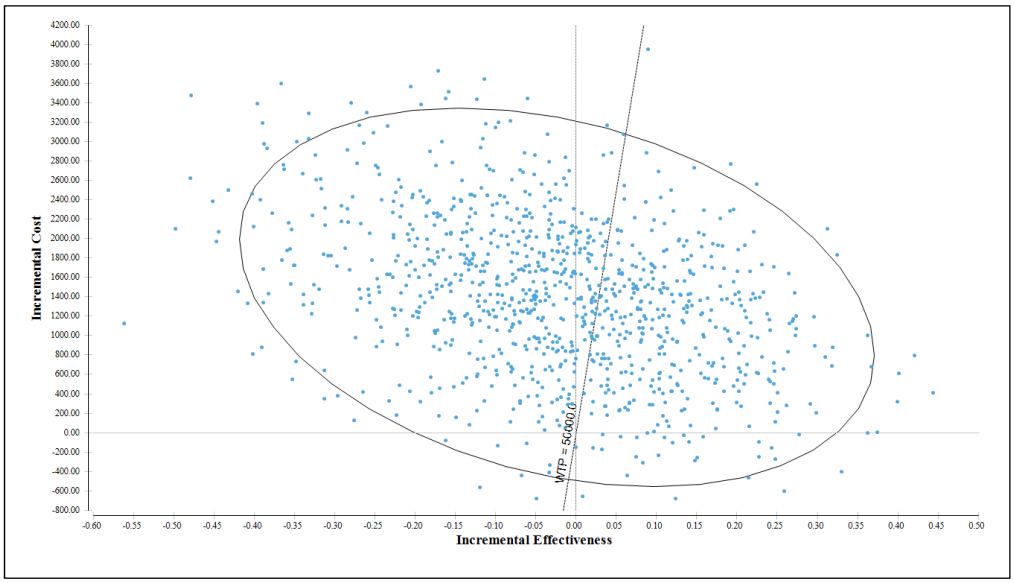
WTP = willingness-to-pay.

Figure 31: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 2 — Reference Case (Alberta Perspective)



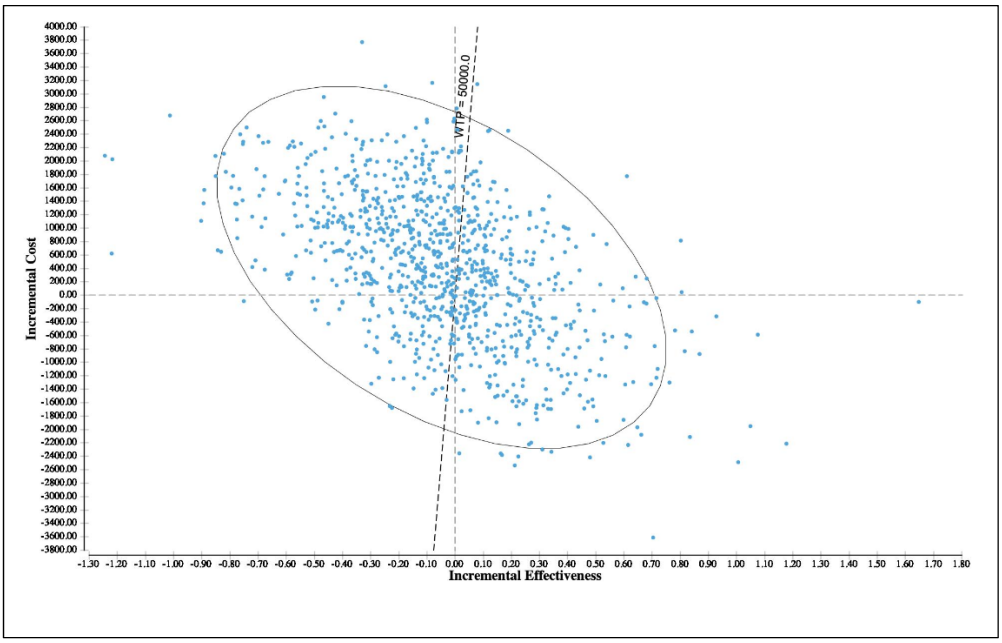
WTP = willingness-to-pay.

Figure 32: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 2 — Ontario Perspective



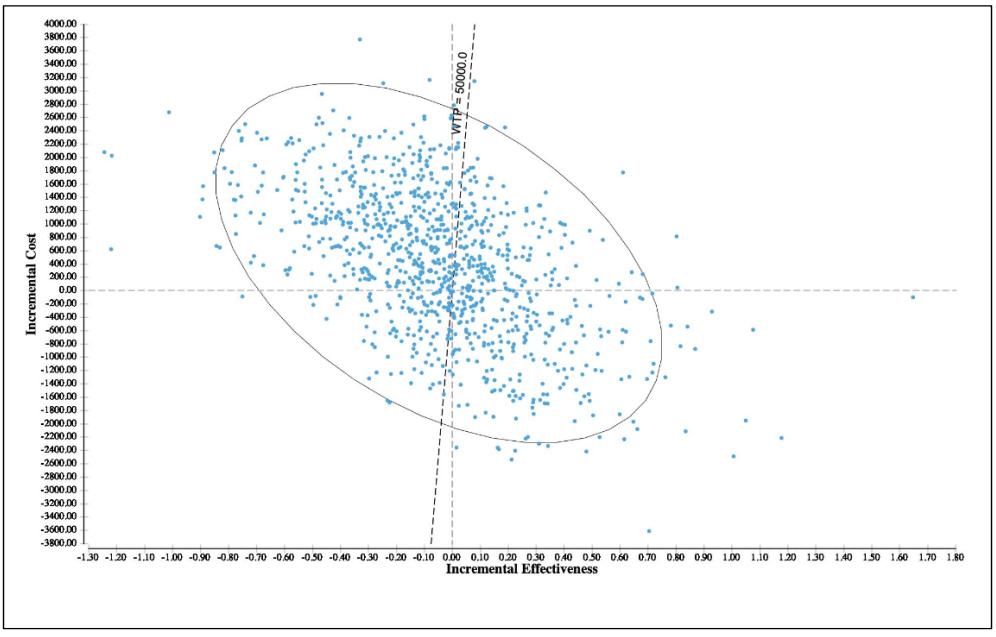
WTP = willingness-to-pay.

Figure 33: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 3a — Reference Case (Alberta Perspective), Based on Trabectome



WTP = willingness-to-pay.

Figure 34: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 3a — Ontario Perspective, Based on Trabectome



WTP = willingness-to-pay.

Figure 35: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 3a — Reference Case (Alberta Perspective), Based on iStent Inject

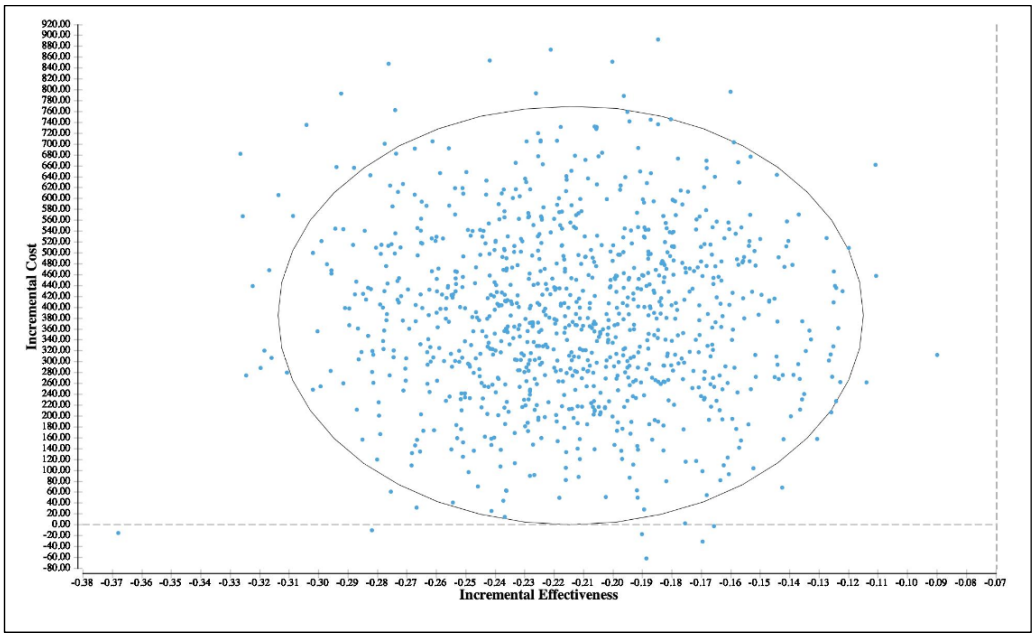
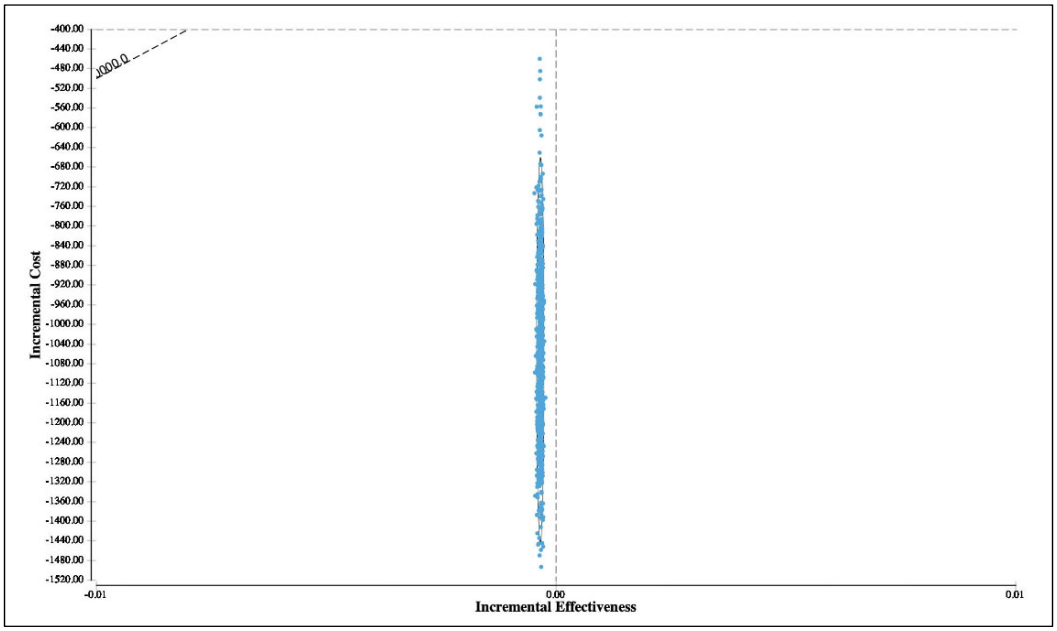
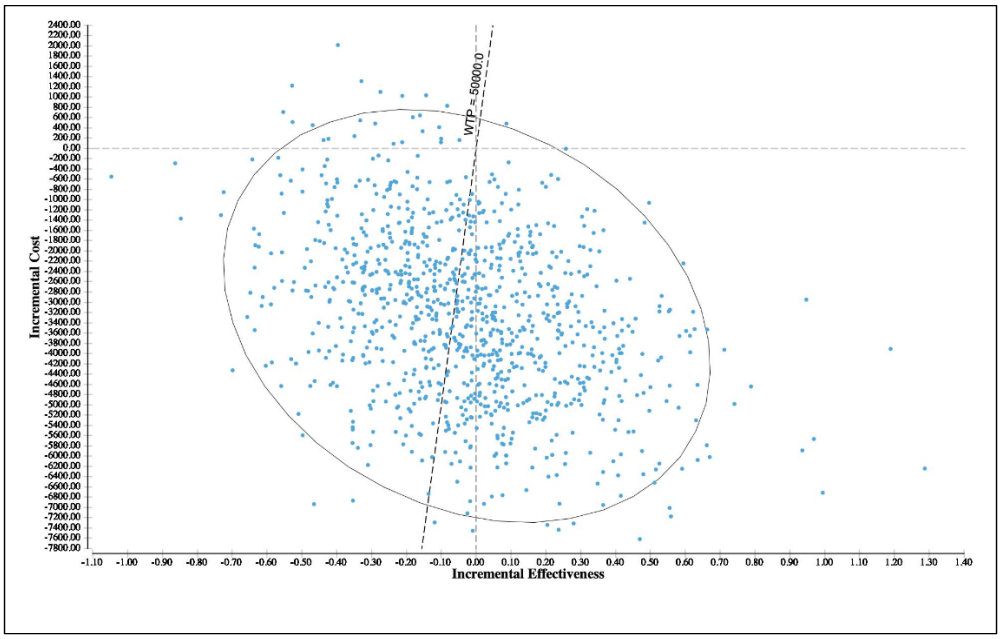


Figure 36: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 3a — Reference Case (Alberta Perspective), Based on XEN 45



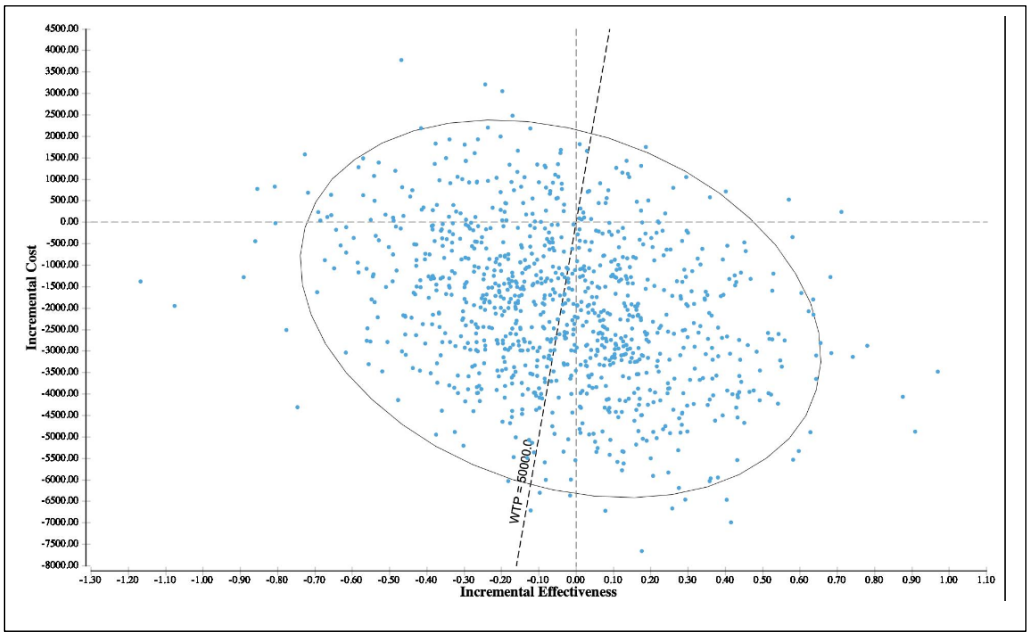
Note: Effectiveness parameters were not defined by a distribution.

Figure 37: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 3b — Reference Case (Alberta Perspective)



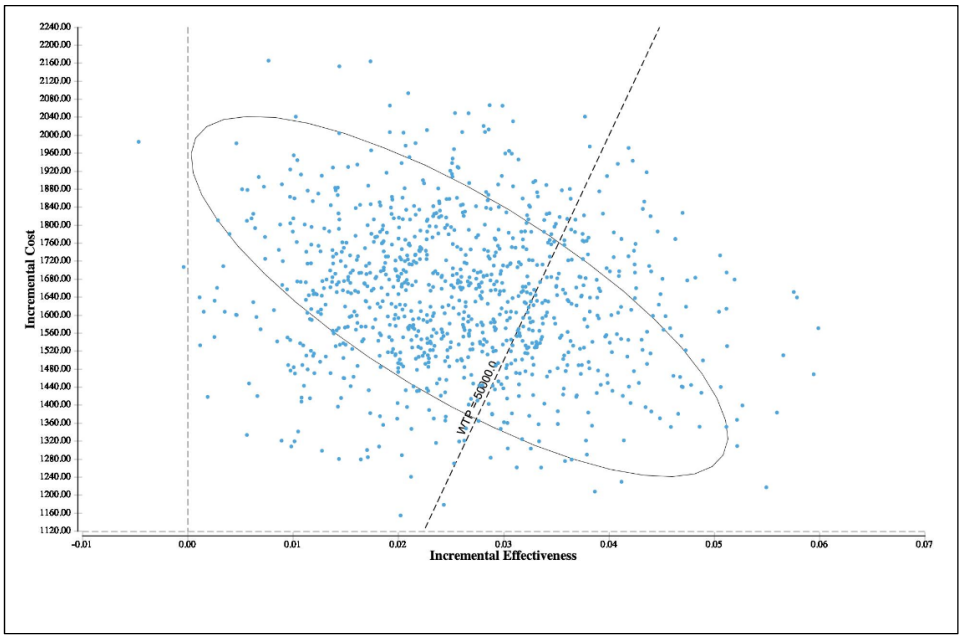
WTP = willingness-to-pay.

Figure 38: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 3b — Ontario Perspective



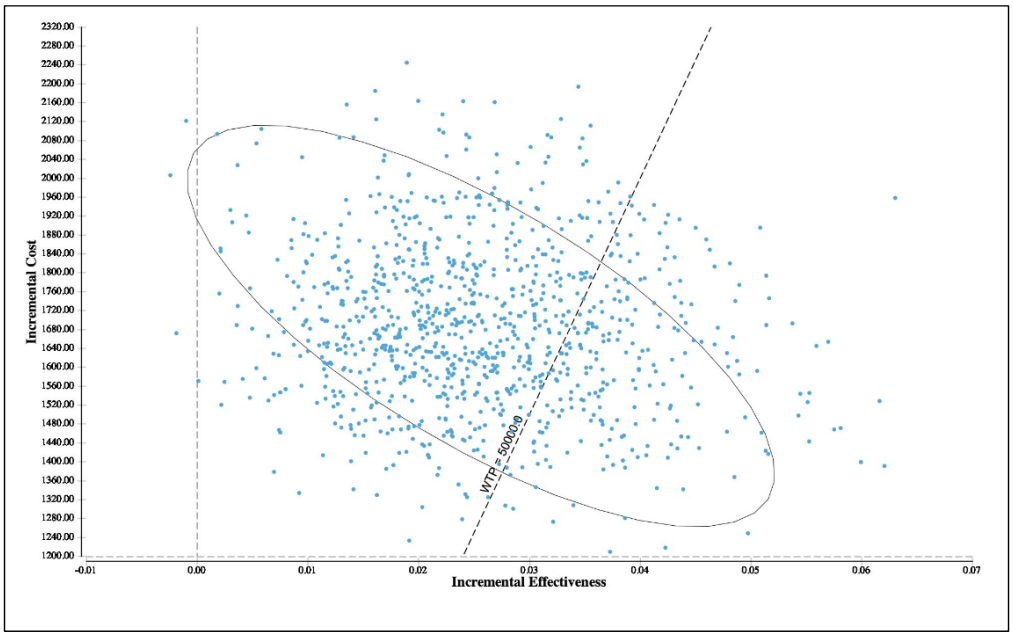
WTP = willingness-to-pay.

Figure 39: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 4 — Reference Case (Alberta Perspective), Based on Hydrus Microstent + Cataract Surgery



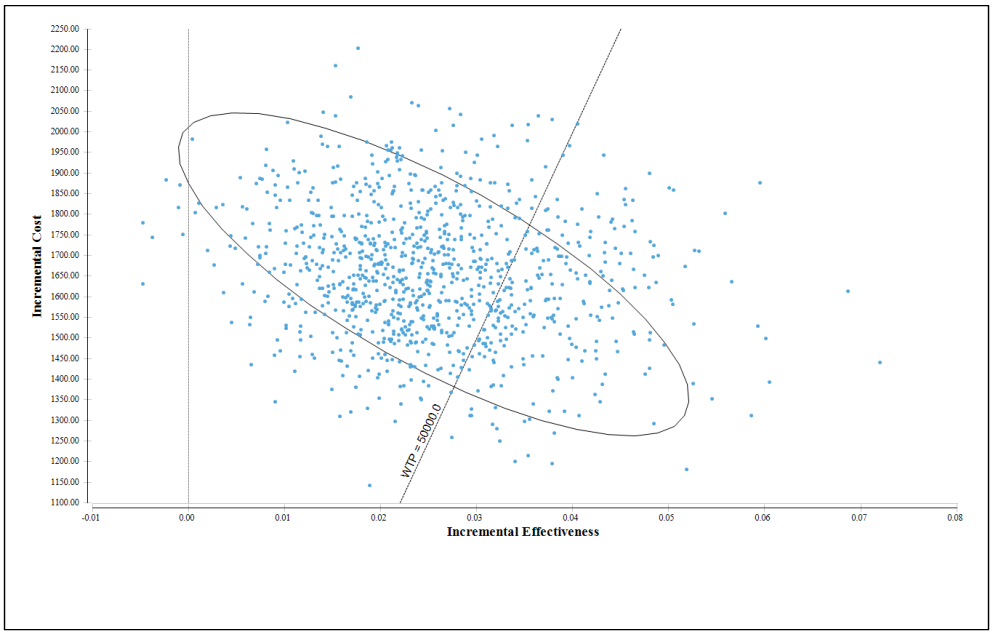
WTP = willingness-to-pay.

Figure 40: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 4 — Ontario Perspective, Based on Hydrus Microstent + Cataract Surgery



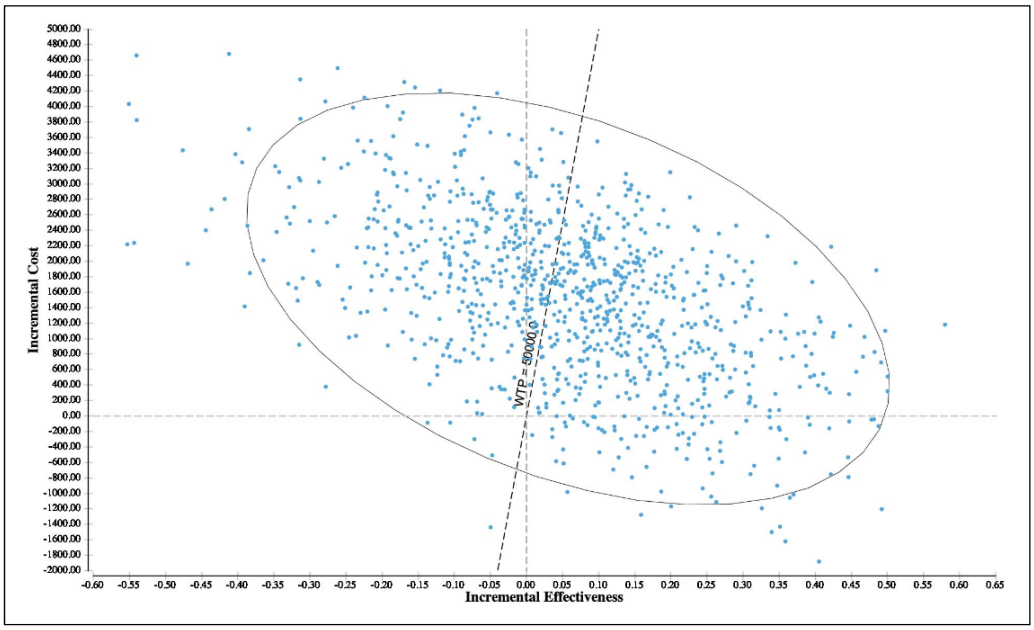
WTP = willingness-to-pay.

Figure 41: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 4 — Reference Case (Alberta Perspective), Based on iStent Inject+ Cataract Surgery



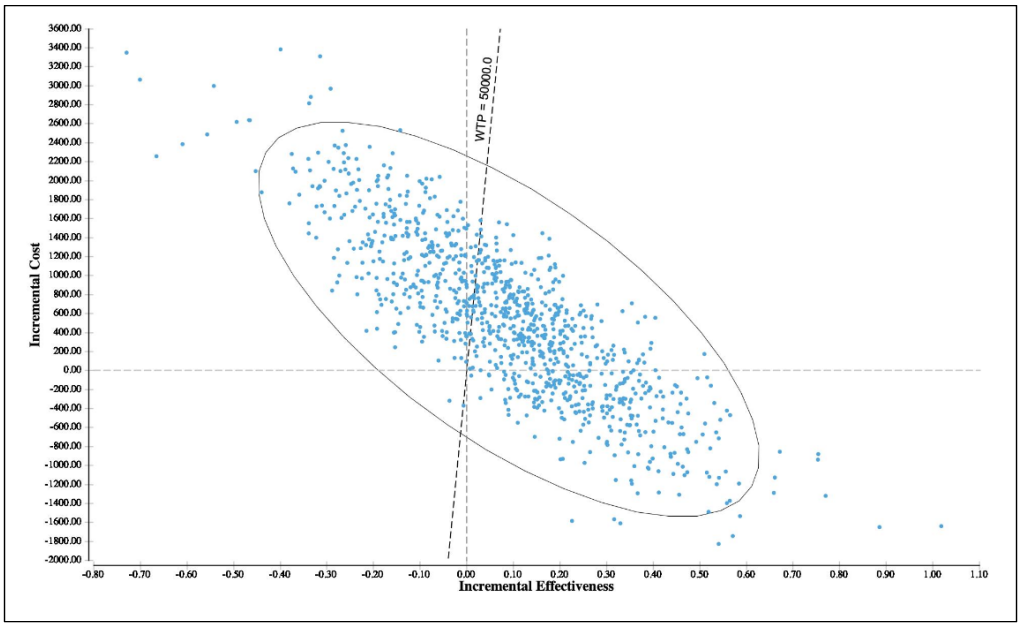
WTP = willingness-to-pay.

Figure 42: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 4 — Reference Case (Alberta Perspective), Based on CyPass Micro-Stent + Cataract Surgery



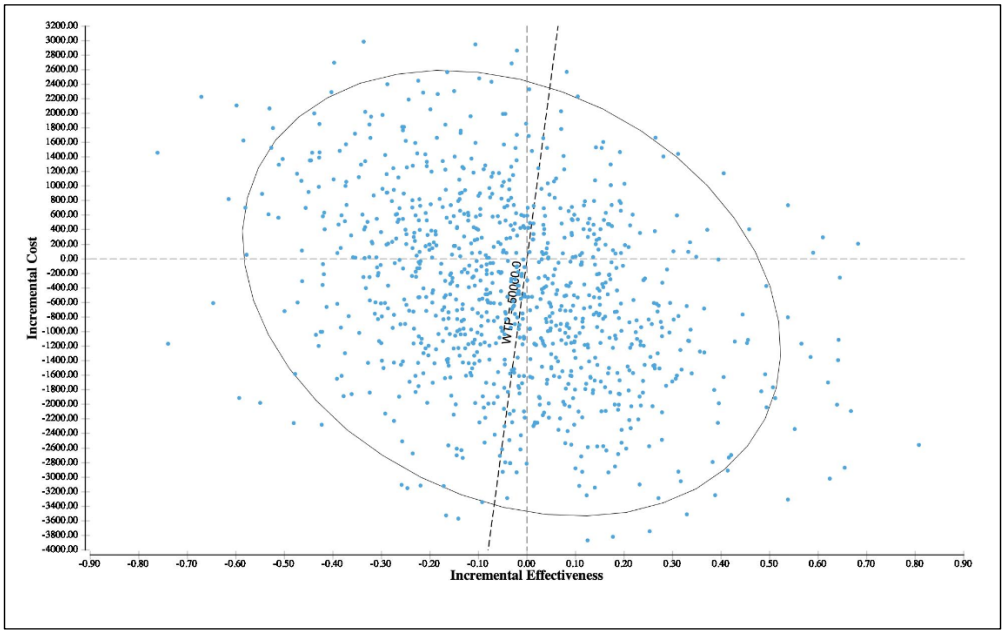
WTP = willingness-to-pay.

Figure 43: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 4 — Reference Case (Alberta Perspective), Based on ECP + Cataract Surgery



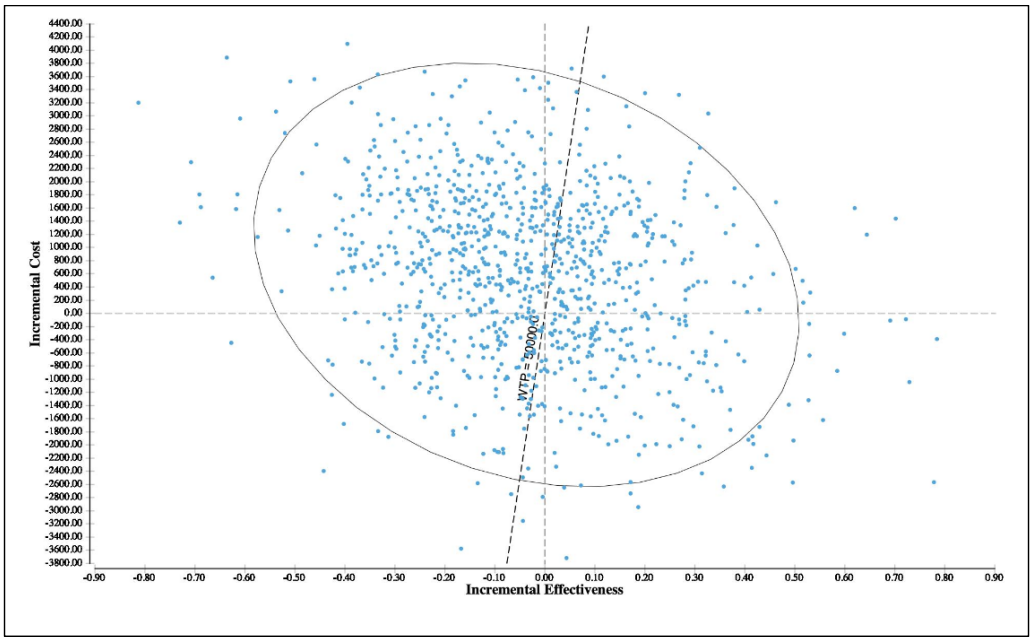
ECP = endoscopic cyclophotocoagulation; WTP = willingness-to-pay.

Figure 44: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 5 — Reference Case (Alberta Perspective)



WTP = willingness-to-pay.

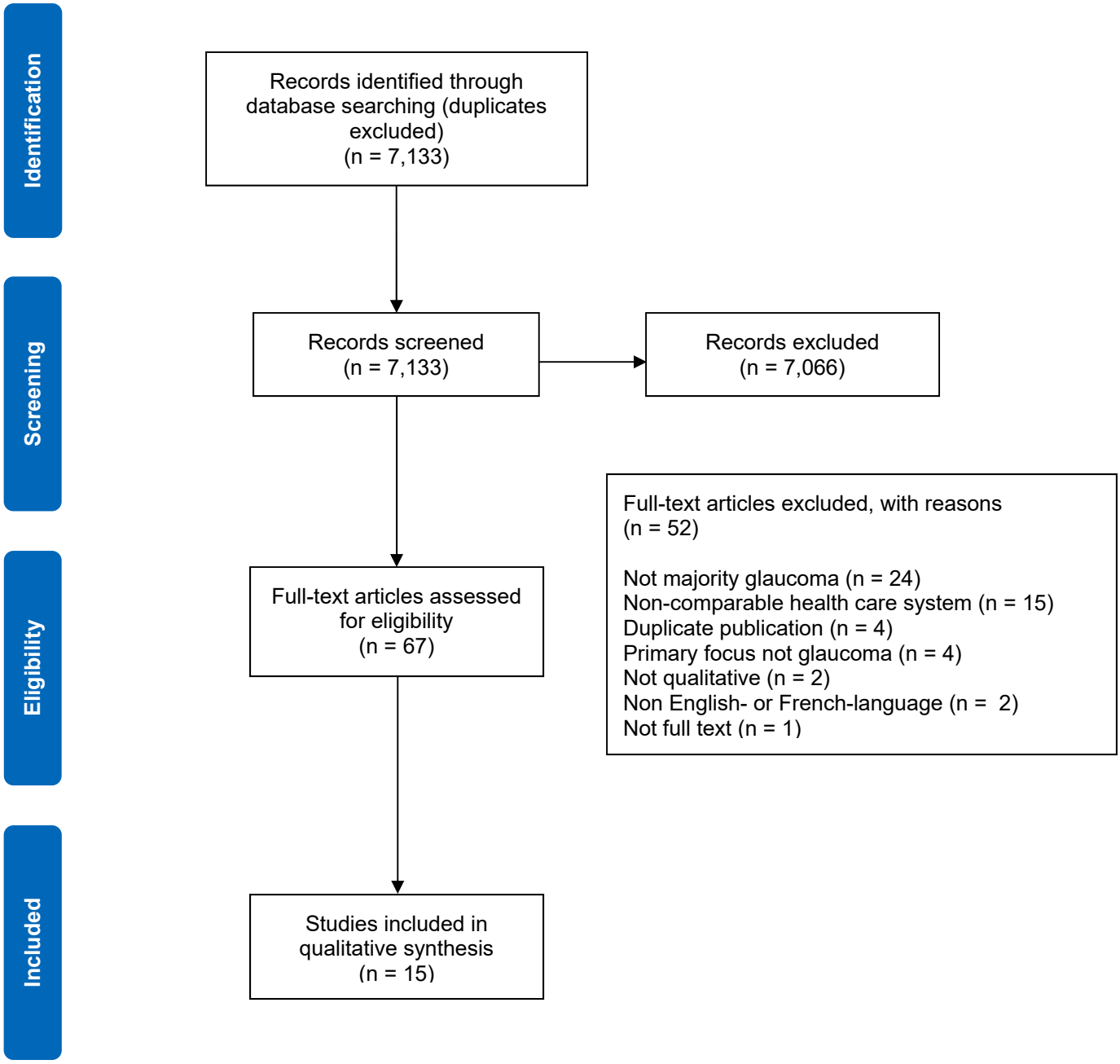
Figure 45: Probabilistic Results on the Incremental Cost-Effectiveness Plane for Model 5 — Ontario Perspective



WTP = willingness-to-pay.

Appendix 17: Study Selection Flow Diagram — Patients' Perspectives and Experiences Review

Figure 46: PRISMA Flowchart of Selected Reports for the Patients' Perspectives and Experiences Review



Appendix 18: Included Studies — Patients' Perspectives and Experiences Review

Table 50: Included Studies in the Patients' Perspectives and Experiences Review

First Author, Publication Year, Country, Funding	Study Objectives	Study Setting	Sample Size	Inclusion Criteria	Data Collection (Type, Sampling Method)	Data Analysis
Taylor, 2002,[142] US, Merck Inc.	To understand the reasons for non-compliance	Patients of two ophthalmologists (one university clinic, one general practice)	28 patients	Patients of an ophthalmologists clinic who had seen 2 or more ophthalmologists and were on 2 or more medications	Focus groups (n = 21) and in-depth interviews (n = 11)	NR
Lacey, 2009,[133] UK, Norwich Glaucoma Research Fund	To explore patients' experiences of barriers to adhering to glaucoma medications	Two ophthalmologist clinics in the UK	24 patients	Patients with moderate/severe POAG, taking 2 or more medications for glaucoma, visual acuity of > = 6/12, having had consulted with 2 or more ophthalmologists, and diagnosed with glaucoma for > 1 year	Focus groups (n = 24) and semi-structured interviews (n = 10)	Framework analysis
Green, 2002,[134] UK, Moorfields Eye Hospital Trustees	To explore the meaning of symptoms for people living with moderate-to-severe glaucoma	One specialist urban eye hospital and one general regional hospital	28 patients	Moderately severe or severe OAG	In-depth interviews (n = 20), group interviews (n = 8)	Constant comparative method
Kugelmann, 1983,[143] US, NR	To develop a phenomenology of glaucoma as an illness	Specialist glaucoma clinic at a regional ophthalmology centre	31 patients	NR	Interviews	Phenomenology
Lunnela, 2010,[147] Finland, the Union of Health and Social Care Professionals, Finland	To understand the views of compliant patients with glaucoma to patient education and social support	Outpatient eye clinic at central hospital	12 patients	Patients with glaucoma and with "good compliance" (not defined)	Semi-structured interviews	Content analysis

First Author, Publication Year, Country, Funding	Study Objectives	Study Setting	Sample Size	Inclusion Criteria	Data Collection (Type, Sampling Method)	Data Analysis
Cross, 2009,[135] UK, Birmingham Strategic Health Authority; Heart of Birmingham Teaching Primary Care Trust; City Hospital NHS Trust; Pfizer UK; Birmingham Social Service	To explore the experience of African-Caribbean patients who had undergone filtration surgery for their glaucoma	Outpatient eye clinic at central hospital	8 patients	African-Caribbean patients who had undergone filtration surgery for their glaucoma	Semi-structured interviews	Narrative analysis
Nordmann, 2007,[146] France and UK	To develop a questionnaire to assess patient satisfaction and compliance with glaucoma eye drops	Ophthalmologist practices in France and UK	20 participants (5 clinicians, 15 patients)	Patients with elevated IOP or primary open-angle glaucoma	Semi-structured interviews	Interpretative phenomenological analysis
Leighton, 2012,[136] UK, International Glaucoma Association	To understand the attitudes of patients toward participating in an RCT comparing pharmacotherapy to surgery for advanced glaucoma	Glaucoma clinic, UK	29 patients	Patients with advanced glaucoma, defined as > 15 dB loss on Humphrey visual field tests in at least one eye	Focus groups	Thematic analysis
Prior, 2013,[138] UK, Medical Research Council	To explore the experiences of patients diagnosed with advanced glaucoma	2 outpatient eye clinics, UK	11 patients	Patients with advanced glaucoma, defined as visual field loss of > −20 dB in at least one eye, or bilateral loss of ≥ −12 dB in both eyes	Semi-structured interviews	Directed content analysis
Newman-Casey, 2016,[144] US, Glaucoma Research Foundation, National Institute of Health	To explore patients' beliefs regarding vision loss from glaucoma even with the availability of effective treatment	Tertiary care academic medical centres in three US cities (Los Angeles, CA; Rochester, MN; Durham, NC)	56 patients	Patients with glaucoma	Focus groups	Content analysis

First Author, Publication Year, Country, Funding	Study Objectives	Study Setting	Sample Size	Inclusion Criteria	Data Collection (Type, Sampling Method)	Data Analysis
Shtein, 2016,[145] US, Glaucoma Research Foundation	To describe the role family and friends in the clinical care of patients with glaucoma	Tertiary care academic medical centres in three US cities (Los Angeles, CA; Rochester, MN; Durham, NC)	31 participants (family members)	Family members of patients with glaucoma	Focus groups	Content analysis
Glen, 2014,[137] UK	To explore patients' views on visual field testing and follow-up care	3 outpatient eye clinics, UK	28 patients	Patients attending routine glaucoma care from an ophthalmologist and who had received glaucoma care for > 2 years	Focus groups	Framework analysis
Glen, 2015,[140] UK, Allergan Ltd.	To understand the ways patients with glaucoma cope with vision loss	Members of the public recruited through newsletter of the International Glaucoma Association (charity)	16 patients	Patients with a diagnosis of glaucoma and who had received glaucoma care for > 5 years in the UK	Semi-structured interviews	Framework analysis
Vieira, 2015,[148] Brazil, not stated	To explore patients' views on types of treatment (medical vs. surgical)	Private clinic specializing in glaucoma	18 patients	10 undergoing anti-glaucoma eye drops, 10 who had surgery in the last 12 months or more	Focus groups	Content analysis
Burns, 2001,[141] England	To understand the experiences of patients with suspected glaucoma	Outpatient glaucoma clinic, London	25 patients	Patients with glaucoma	Semi-structured interviews and focus groups	Framework approach

dB = decibel; IOP = intraocular pressure; NR = not reported; OAG = open-angle glaucoma; POAG = primary open-angle glaucoma; RCT = randomized controlled trial; vs. = versus.

Appendix 19: Participant Characteristics From Included Studies — Patients' Perspectives and Experiences Review

Table 51: Characteristics of Participants From Included Studies in the Patients' Perspectives and Experiences Review

First Author, Publication Year	Sample Size	Sex (% Male)	Age Range in Years	Vision Characteristics (Stage of Glaucoma, Vision Score)	Time Since Diagnosis	Occupational Status
Taylor, 2002[142]	28 patients	39%	mid-40s to mid-80s	On at least 2 glaucoma medications	NR	~33% still employed
Lacey, 2009[133]	24 patients	50%	50+	Moderate/advanced POAG, visual acuity > 6/12	> 1 year	33% working
Green, 2002[134]	28 patients	50%	25 to 86	Moderately severe or severe OAG	from 1 month to 20 years	NR
Kugelmann, 1983[143]	31 patients	NR	NR	NR	"long periods of time"	NR
Lunnela, 2010[147]	12 patients	42%	43 to 80	Patients with glaucoma who had "good compliance"	58% had glaucoma >5 years; range 1 to 28 years	NR
Cross, 2009[135]	8 patients	NR	NR	Post-Trabeculectomy African-Caribbean patients	NR	NR
Nordmann, 2007[146]	15 patients and 5 clinicians	53%	50 to 82	7 had elevated IOP, 8 had POAG	mean 16 years (French patients only)	20% working
Leighton, 2012[136]	29 patients	79%	NR	>15 dB loss on Humphrey visual field tests in at least one eye	NR	NR
Prior, 2013[138]	11 patients	36%	Self-reported < 40 to > 70	NR	4 to 16 years (range)	NR
Newman-Casey, 2016[a144]	56 patients	54%	43 to 90	31 had "good" vision (> 20/40 vision in both eyes and AGIS score on visual fields of 6 or less in the worse eye) 25 had "poor" vision (legally blind in one or both eyes, vison worse than 20/2000, or a visual field of 10% or less)	NR	NR
Shtein, 2016[a145]	31 family members and	39%	NR	Some family members and	NA	NR

First Author, Publication Year	Sample Size	Sex (% Male)	Age Range in Years	Vision Characteristics (Stage of Glaucoma, Vision Score)	Time Since Diagnosis	Occupational Status
	friends			friends also had glaucoma, details not reported		
Glen, 2014[137]	28 patients	46%	74 (mean)	NR	> 2 years	NR
Glen, 2015[140]	16 patients	50%	71 (median); IQR 68 to 77	Measurable visual field loss in at least one eye	21 years (median); range 6 to 29 years	NR
Vieira, 2015[148]	18 patients	39%	47 to 93	Patients with advanced-stage primary open-angle glaucoma in at least one eye	NR	NR
Burns, 2001[141]	25 patients	32%	47 to 80	Patients referred to a glaucoma clinic for suspected glaucoma by general practitioners or ophthalmologists	NA	NR

AGIS = Advanced Glaucoma Intervention Study; dB = decibel; IQR = inter-quartile range; OAG = open-angle glaucoma; POAG = primary open-angle glaucoma; NA = not available; NR = not reported.

[a] Same study, unique publication (data, analysis).

Appendix 20: Quality Assessment of Included Studies — Patients' Perspectives and Experiences Review

Table 52: Quality Appraisal of Included Qualitative Studies

First Author, Publication Year	Is the Study Credible?	Is the Study Trustworthy (Dependable and Confirmable)?	Is the Study Relevant (Are the Findings Transferable)?
Burns, 2001[141]	Partially. While the study has a number of limitations (including lack of literature review) and no qualitative approach, they do use data collection methods that collect rich data and findings are supported by data.	Yes. A number of methodological choices support the credibility of the study, including data collection at numerous time points. Analysis is of limited depth, however, thoughtful.	Yes. The study explores what people who have been sent to glaucoma screening think about their potential glaucoma. While the analysis lacks depth in places, the study adds useful insight to the policy question and is consistent with patterns across the studies.
Cross, 2009[135]	Partially. This is a narrative analysis of in-depth interviews. The authors present data from three interviews — following the development and components of a story. It is unclear how the other interviews were used and what was missed.	Partially. As the findings are very descriptive (non-interpretive) it is likely the data would hold true in other settings. It is possible, however, that the analysis could change if the work was more theoretically (or empirically) grounded. The analysis demonstrates depth, although no signposts for reflexivity.	Yes. As the only study focusing on African-Caribbean patients, this study adds to knowledge of the health care experiences of marginalized or racialized patients.
Glen, 2014[137]	Partially. The study goes through the mechanics of qualitative research (using reporting guidelines) but the analysis is thin and attends to worries of "bias" (as opposed to reflexivity). The analysis uses a framework approach to identify themes that are under developed, as categories or concepts and have overlap. The authors did not look for alternative explanations/cases.	Partially. While the data are trustworthy, the analysis is not due to underdeveloped coding and themes.	No. The results are very specific to visual field testing, a very specific test that bears marginally on MIGS. The report provides some details about patients' experiences of health care systems (e.g., wait times, access) that are nominally of interest although highly underdeveloped and presented more like survey information.

First Author, Publication Year	Is the Study Credible?	Is the Study Trustworthy (Dependable and Confirmable)?	Is the Study Relevant (Are the Findings Transferable)?
Glen, 2015[140]	Partially. The study is well reported, following reporting guidelines, and as such, pays attention to methodological details. The analysis is underdeveloped and relies heavily on quotes that may lead to alternative interpretations. Non-distinctive (i.e., overlapping) categories were used to organize the data. No details regarding an included figure, and unclear why this was not used to organize findings.	Partially. The study findings are very limited and are largely re-presentation of the data. The data themselves could be analyzed for this review, but it is noted that there are things "missing" from the analysis.	Partially. To a limited extent, the findings support the patterns across studies; however, it is less clear what these patterns mean — for glaucoma, for patients.
Green, 2002[134]	Yes. This study begins by grounding the inquiry in both medical and social models of glaucoma and disability, and as such, is theoretically situated. Methods include constant comparative method, and the results indicate that the authors interpreted what they heard (i.e., did not take at face value).	Yes. Within each theme, the authors describe nuances and variations in peoples' experience of glaucoma; this variation draws attention to points of difference and the ways in which they are accounted for by social position (role, economic, etc.) of the individual. One limitation is that the authors do not describe the role of comorbidities, even as they acknowledge work that points to the ways that slight loss is experienced relative to other conditions.	Yes. As this is theoretically grounded and the study findings are well-described and their interconnections explored, this study is very relevant to the current policy problem. One consideration to bear in mind is the differences in the length of time since diagnosis; as the authors did not report median (only range), and as such it is difficult to assess how this might affect perceptions of the condition.
Kugelmann, 1983[143]	Partially. This study is a phenomenological approach to glaucoma and looks at the experience of glaucoma from how selves perceive glaucoma and how glaucoma affects selves using metaphors to describe the results. At times, the metaphors (and their sub interpretations) feel forced, or poorly placed. No description was provided of analytic methods, other than the use of metaphors, which raises the question of how discrepant data were accounted for and what may have been left out.	Partially. Poor reporting of the analytic methods make trustworthiness difficult to assess. Read in the context of the entire body of the evidence, there is some support for the reported findings; however, the use of metaphors was not entirely persuasive. Lack of details about the respondents also questions how likely these findings hold across people.	Partially. Although interesting observations that move beyond the data, caution is warranted given poor reporting of methods and participant characteristics.

First Author, Publication Year	Is the Study Credible?	Is the Study Trustworthy (Dependable and Confirmable)?	Is the Study Relevant (Are the Findings Transferable)?
Lacey, 2009[133]	Partially. This is a highly descriptive study, which focused on barriers to adherence as conceived in the literature. As such, the interview guide directed a very specific line of inquiry. However, this is consistent with their overall approach of framework analysis. Limited data are provided, and authors checked to assess data "reliability." Used interview and focus groups as forms of data collection, and authors note difference in the data, showing some reflexivity.	Partially. The results are thin; however, can be trusted as a descriptive summary of what people said in the interviews and focus groups. Limited and decontextualized codes provided in Table 1 prevent an assessment of whether the results are grounded in the data. Some primary conclusions i.e., "what motivates patients to be adherence" are not supported by data collection or analysis.	Partially. The findings are transferable as a description of patients' views on what barriers are, within a biomedical paradigm.
Leighton, 2012[136]	No. This is a highly descriptive study that collected thin data through focus groups and that summarizes key (frequent) themes, as a supplement to an RCT.	No. While the data are trustworthy, the data analysis require more corroboration and to move beyond the data.	Partially. Some results are reported that relate to patients' perspectives on MIGS; however, as the study was conducted as part of a trial, the transferability of results are unclear. A lack of reporting of participant details further calls transferability into question.
Lunnela, 2010[147]	No. This study starts with the premise that compliance is an active engagement and responsibility of patients. The authors interview patients with "good compliance" regarding their views of patient education and social support. The reported themes are domains of the interventions (e.g., timing of education, types of social support), which leads to a thin summary and grouping of the views of patients. The authors did not examine the data for possible contradictions or negative cases.	No. Given the orientation of the study, it is unclear if the findings exist independently of the researchers' orientation toward compliance, thus making it unclear if the findings are dependable. While the data are trustworthy, it is unclear if the results are trustworthy.	Partially. The thin analysis reads as a summary of data points. Given the study population includes patients with "good compliance" (undefined) it is uncertain that these results would apply across patients with varying degrees compliance. Regardless, some of the data resonates with the larger body of evidence, supporting some degree of transferability and relevance to this review.

First Author, Publication Year	Is the Study Credible?	Is the Study Trustworthy (Dependable and Confirmable)?	Is the Study Relevant (Are the Findings Transferable)?
Newman-Casey, 2016[144]	No. This study uses qualitative data (focus groups) and a frequentist approach to content analysis (described as semi-quantitative). Key details in sample selection are missing. The research objective (i.e., identifying barriers to preventing vision loss in glaucoma) is mismatched to the research question (i.e., why patients believe that glaucoma continues to cause vision loss despite the availability of effective treatment). The authors' level of experience with qualitative research is unclear.	No. The study is not grounded in the literature (qualitative or quantitative) on treatment barriers in glaucoma. The findings are a summary and aggregation of data categories, with no analysis. It is likely that the data can be viewed as "trustworthy," although provide limited insight into the meaning or understanding of glaucoma or its treatment.	Partially. The findings are descriptive and as such are likely transferable; however, a lack of credibility and dependability make it difficult to assess what results specifically would be transferable.
Nordmann, 2007[146]	No. Key results are not supported by data. A limited description of the study methods make it difficult to assess how the authors moved from data to results. While some data are relevant to this inquiry, the analysis is somewhat unorganized.	No. While the data are likely trustworthy, concepts around compliance and satisfaction are not well explored.	Partially. Given the limited exploration of specified concepts, it is likely that the analysis would not hold in other contexts. Given the prominence of patient-reported difficulties with eye drops, this analysis is relevant to the current review.
Prior, 2013[138]	Partially. The study uses directed content analysis to identify barriers to late diagnosis; however, does not explore patients' description in much depth. the authors do not provide evidence of reflexivity or attempts to push the analysis beyond the data.	Partially. Given the descriptive nature of the analysis, it is likely that the data are trustworthy, although the analysis including emergent codes and themes are underdeveloped.	Partially. The thin description of patients' experience is largely focused on how people were diagnosed, as opposed to how people were impacted by the diagnosis. The identification of identify system-level barriers to diagnosis is relevant for the current review.
Shtein, 2016[145]	No. These data are from the same study as Newman-Casey, 2016. The starting point of the study is of questionable use: asking family members about their role in supporting patients, as opposed to asking for their understanding of their role.	No. Limited reporting about study and participant characteristics challenge an assessment of trustworthiness.	Partially. Considered alongside the whole body of evidence, some data presented in this report support other observations, and should be interpreted in light of other analyses.

First Author, Publication Year	Is the Study Credible?	Is the Study Trustworthy (Dependable and Confirmable)?	Is the Study Relevant (Are the Findings Transferable)?
Taylor, 2002[142]	No. No description of data analysis provided, and it does not appear that an appropriate qualitative approach was used. The authors refer at times to external literature; however, primarily to identify research gaps. The authors identify using external researchers to explore how the position of the researchers might have affected participants' responsiveness. The study begins from the place that patients do not comply with eye drops, and implies that they should, in order to probe reasons for non-compliance. It appears that pre-set ideas around compliance drove the investigation, with little for emergent ideas.	Partially. The questions asked were somewhat directed and did not give much space for the participants' own voice and ideas on non-compliance. Some insight is shown regarding participants' reporting of their condition demonstrating a move beyond data and toward an analysis, for example, noting that patients say side effects don't matter, although they readily complain about them.	Partially. Some interesting insights provided regarding patients' stated perceptions and actual experiences, however results are primarily an aggregative of what participants said. There is limited probing into understanding reported experiences, meaning that some caution is warranted and the results should be interpreted in light of the entire body of evidence.
Vieira, 2015[148]	No. While the authors report that there is no evidence related to treatment preferences in the literature, they missed the opportunity to draw on the many studies on adherence. Although it is reported that semi-structured interviews were used, there is no further information provided regarding sampling, methods of analysis, or findings.	No. Within the results, descriptive and thin results are presented regarding: patients' common experiences; however, some more analytic findings are presented in the discussion section (see transferability), making it unclear how these ideas were developed. The analysis is descriptive, using content analysis to identify themes, and no work is done to move beyond the data.	Partially. The results show that key concepts were pulled out and described to a good extent; however, with a thin and descriptive analysis the study does little to add to an understanding of the meaning of glaucoma in patients' lives, and life after surgery.