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CADTH OPTIMAL USE REPORT

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

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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.

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Table of Contents

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 primary glaucoma, which occurs without a known cause, 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] Secondary glaucoma occurs when there is a known cause.[8,9]

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;[1,10] for every 1 mm Hg increase in IOP, there is a 10% higher risk of both development and progression of glaucoma.[11] 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 suboptimally; angle-closure glaucoma occurs when the fluid draining system is anatomically blocked.[8] OAG represents the most common form of the condition.[4,12]

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.[8,13] 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.[14,15] Challenges associated with pharmacotherapy include ineffective use (e.g., under- or overdosing, incorrect timing, or administration),[16,17] local or systemic side effects (e.g., irritation) or toxicity,[18,19] and considerable lifetime costs.[20] Laser surgery may be less effective than pharmacotherapy, and can be associated with ocular discomfort, IOP spikes, and the need for repeat procedures.[21,22] Although filtration surgeries are well established and generally effective,[23] 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),[4,14,24,25] have a long recovery period,[26] and, because of their invasive nature, may affect subsequent surgery due to scar tissue formation if required.[24] 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.[24,27] 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.[14,27-30] The FDA and the American Glaucoma Society (AGS) 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.[31-33] Other definitions[24,30] are generally consistent with the FDA-AGS definition, though they may differ in some aspects (e.g., inclusion of ab interno devices and procedures only).[24] Regardless, certain features and qualities are commonly associated with MIGS devices and procedures, including the following:

- They are expected 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 stand-alone 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 intraocular lenses.[13,14,20,24,27,28,33]

Generally, MIGS devices and procedures are aimed at, and evaluated by, OAG patients.[27,29,34-36] 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.[23,37] The characteristics of patients for whom MIGS devices and procedures would be most clinically effective, cost-effective, and acceptable remain to be established.

There are currently 10 MIGS devices and procedures approved for use in Canada (see Appendix 1). 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), using a device (i.e., iStent and iStent Inject), or via 360º suture (i.e., gonioscopy-assisted transluminal trabeculotomy [GATT]); increasing uveoscleral outflow via suprachoroidal shunts (i.e., CyPass Micro-stent), or 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 (i.e., phacoemulsification), which also independently lowers IOP.[32]

In general, there is growing demand for and use of MIGS.[28,37] However, the cost of MIGS can be considerable, and coverage under the public health insurance plans is inconsistent across jurisdictions.[38] Therefore, there is a need to clarify current policy on access and reimbursement related to MIGS devices and procedures.

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

The purpose of this Health Technology Assessment (HTA) is to address the policy questions through an assessment of the clinical effectiveness and safety, cost-effectiveness, patient perspectives and experiences, ethical issues, and implementation issues of MIGS devices

and procedures for adults with glaucoma. An analytical framework can be found in Appendix 2.

Research Questions

The proposed HTA will address 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 Analysis

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?

Patient 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?

Methods

This protocol was written a priori and will be followed throughout the study process. Any deviations from the protocol will be disclosed in the final report, and updates will be made to the PROSPERO submission accordingly (registration number: CRD42018082223). Research questions 1 to 4 will be addressed by a de novo systematic review of published clinical evidence.

Clinical Review

The protocol for the clinical review has been developed in consideration of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist[39] for guidance on clarity and completeness. The clinical review will address the following 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?

Literature Search Strategy

The literature search will be performed by an information specialist using a using a peer-reviewed search strategy. The clinical search strategy is presented in

Information will be 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 will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be glaucoma, minimally invasive glaucoma surgery, and minimally invasive glaucoma surgical devices.

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

The initial searches were completed by November 2017. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be 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 will be incorporated into the analysis of the final report. Any studies that are identified after the stakeholder feedback period will be 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) will be 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 (SR) 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 will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Study Design

An informal scoping review of existing HTAs, SRs, primary clinical studies (including both randomized and non-randomized studies), and evidence-based guidelines, supported by a Rapid Response Reference List (i.e., a comprehensive list of relevant publications within the past five years),[40] was conducted to inform the preparation of this protocol. In this scoping review, although six recent SRs[1,29,31,34,41,42] were identified, they did not capture all of the most recent primary clinical studies or evidence for all of the MIGS that are approved for use in Canada. In addition, most SRs focused on a single MIGS procedure or device, and on a specific subgroup of patients with glaucoma (i.e., more narrow than the population of interest for the present clinical review). Therefore, to ensure inclusion of all relevant primary studies, and to enable examination of different subgroups of interest, it was decided that conducting a de novo SR of primary studies would be the most appropriate approach for CADTH to address the comparative clinical effectiveness and safety of MIGS for adults with glaucoma.

Study Eligibility

The eligibility criteria for the clinical research questions can be found in Table 1.

Table 1: Eligibility Criteria for Clinical Research Questions

Population
Adults (i.e., mean age of ≥ 18 years) with acquired 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 1-2:
• 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)
  ○ Approach: Increasing trabecular outflow by bypassing the TM via 360º suture
  ▪ GATT
  ○ Approach: Increasing uveoscleral outflow via suprachoroidal shunts
  ▪ CyPass Micro-Stent
  ○ Approach: Creating a subconjunctival pathway for filtration
  ▪ XEN 45 Gel Stent
  ▪ XEN 63 Gel Stent
  ▪ XEN 140 Gel Stent
 	
Questions 3-4:
• The above MIGS devices and procedures performed in combination with cataract surgery (i.e., phacoemulsification)

Comparators
Questions 1-2: • A different[b] 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 3-4:** • A different MIGS device or procedure performed in combination with cataract surgery (i.e., MIGS plus phacoemulsification) • Filtration surgery performed in combination with cataract surgery (i.e., phacotrabeculectomy) • Cataract surgery (i.e., phacoemulsification) alone
Outcomes[c]
Questions 1, 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, 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[d] • 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, or endocyclophotocoagulation; GATT = gonioscopy-assisted transluminal trabeculotomy; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; QoL = quality of life; TM = trabecular meshwork.
[a] MIGS devices and procedures that are approved for use by Health Canada are eligible for inclusion.
[b] "A different MIGS" means any MIGS device or procedure compared with any other MIGS device or procedure (i.e., MIGS compared with each other).
[c] All outcomes are considered to be of "critical" importance[43] based on the informal scoping review that informed this project and on consultation with a clinical expert.
[d] Cohort studies are defined as studies in which participants are sampled on the basis of exposure and in which outcomes are assessed in a follow-up.[44] 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.[44] Only study designs providing comparative evidence are eligible for inclusion.

Studies will be included if they are published in English or French and meet the selection criteria in Table 1.

Studies with mixed populations, that is, comprising both individuals who meet and those who do not meet the eligibility criteria, will be included if the results pertaining to the population of interest are reported separately. If results for the population of interest are not reported separately, studies with a mixed population will be included if 80% or more of the population meet the inclusion criteria. The criteria used to assess glaucoma severity in the included studies will be clearly reported where possible.

Regarding interventions specifically, devices not approved and indicated for MIGS according to the Medical Devices Active Licence Listing]at the time of protocol development will be excluded. If there are multiple publications from the same study, the older publications will be excluded, unless they provide additional information on outcomes of interest.

Literature Screening and Selection

Two reviewers will independently screen titles and abstracts of all citations retrieved against eligibility criteria (see Table 1). Exclusion by both reviewers will be required for a record to be excluded at the title and abstract level. Full-text versions of all other articles will be retrieved for the second level of screening. The same reviewers will independently examine all full-text articles, and consensus will be required for inclusion in the review. Discrepancies between reviewers will be resolved by discussion between the reviewers or by a third reviewer if needed. Study selection will be conducted using DistillerSR using standardized screening forms (see Appendix 4 for a sample screening form).

The list of included studies will be posted online for 10 business days, during which time stakeholders can submit additional publications for consideration. These publications will be

screened against the inclusion criteria by two independent reviewers following the previously described process.

The study selection process will be presented in a PRISMA flowchart.[45] A list of excluded studies, with reasons for exclusion after full-text review, will be provided.

Data Extraction

Data extraction for included studies will be conducted in Microsoft Word using a standardized extraction form (Appendix 5). Relevant information will be extracted, including:

- Study characteristics (e.g., first author's name, publication year, publication title, country where the study was conducted, funding sources)
- Methodology (e.g., study design and objectives, Inclusion and exclusion criteria, recruitment method, primary and secondary outcomes, subgroup analyses of interest)
- Population (e.g., number of patients or eyes, age, sex/gender, race, type of glaucoma, glaucoma severity/stage, 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 regarding the outcomes and subgroups of interest
- To which research question(s) the study is relevant.

Data extraction will be completed by one reviewer and checked for accuracy by a second reviewer. Data from figures will be extracted if explicit numerical data are reported. If relevant data are missing from included studies, attempts will be made to contact the corresponding authors of these studies to obtain missing information.

Quality Assessment: Individual Studies

The risk of bias in primary research studies will be systematically evaluated using the methods described in the Cochrane Risk of Bias assessment tool for randomized controlled trials[46] and the Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool for non-randomized interventions and observational studies.[47] The Cochrane Risk of Bias tool allows for the assessment of seven sources of bias. For each item, a judgment of "low," "high," or "unclear" will be assigned and used to indicate an overall judgment of risk of bias for each study.[46] The ROBINS-I tool allows for the assessment of risk of bias across 34 potential items in seven domains. Each item is answered as "yes," "probably yes," "probably no," "no," and "no information," with "yes" signifying a judgment of low risk of bias and "no" indicating concern with risk of bias. Risk of bias for each domain in each study will be assessed as "low," "moderate," "serious," "critical," or "no information," and will be used to assign an overall judgment to each study using the same classification scheme in accordance with ROBINS-I guidance. The risk of bias assessment will be conducted by two independent reviewers, with any disagreements resolved by discussion with a third reviewer if required.

A narrative summary of the results of the risk of bias assessment for each included study will be provided. Specifically, tables will be developed to present the risk of bias judgments, along with a narrative description of the strengths and limitations of the included studies.

Quality Assessment: Overall Body of Evidence

The quality of evidence for each outcome by each study design will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[48] According to GRADE, evidence from randomized controlled trials (RCTs) begins with a rating of "high" quality, but can be rated down if there is risk of bias,[49] imprecision,[50], inconsistency,[51] indirectness,[52] or publication bias,[53] 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 rated up 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,[54] because these characteristics increase the confidence in the estimated effect. Quality assessments will be performed by one reviewer and verified by a second reviewer, and will be presented in GRADE evidence profile tables.[55] These assessments will be used to provide explicit judgments about the certainty in the evidence.

Data Analysis

Narrative Syntheses

Narrative syntheses will be performed, including the presentation of study characteristics and findings within summary tables. The direction and size of any observed effects will be summarized across studies, including an assessment of the likelihood of clinical benefit (i.e., clinical effectiveness) or harm (i.e., safety).

Meta-Analyses

The results of the included studies will be pooled, using random effects meta-analyses, if data are sufficiently homogeneous in terms of clinical, methodological, and statistical characteristics. Clinical and methodological heterogeneity will be assessed in consultation with clinical experts, and will consider 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 and duration of medication washout period). Separate analyses will be conducted for randomized and non-randomized studies; results from randomized and non-randomized studies will not be pooled.

When deemed appropriate, dichotomous outcomes (e.g., achievement of target IOP) will be pooled using relative risks and 95% confidence intervals (CIs) will be calculated. Continuous outcomes will be pooled using mean differences and corresponding 95% CIs. If adjusted effects measures are reported, the adjusted results will be used in the primary analysis, and differences between unadjusted and adjusted results will be discussed. If required measures of variance are not available, variances will be imputed where possible.[56] If non-parametric data (e.g., medians or quartiles) are reported, parametric data (e.g., means and standard deviations) will be estimated using the methods from Wan et al.[57] Forest plots will be created for individual summary estimates. Meta-analyses will be carried out using the Cochrane Review Manager software (version 5.3, or the most up-to-date version available at the time of analysis).

Unit of Analysis

The unit of analysis will be the participant. For each eligible study, whether randomization was at the level of the participant or the eye will be recorded. If both eyes from a single

participant were included in a trial, whether the analyses accounted for the intra-person correlation will be documented; if the trial did so, the paired analysis data will be used to maintain the participant as the unit of analysis. If the analyses did not account for the intra-person correlation, attempts to do so will be done using the methods in the Cochrane Handbook for Systematic Reviews of Interventions.[58]

Heterogeneity and Subgroup or Meta-Regression Analyses

Statistical heterogeneity will be 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 will be interpreted according to the guidance in the Cochrane handbook, as follows: I^2 values < 40% might not be important, values of 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and ≥ 75% will be interpreted as considerable heterogeneity.[59] Heterogeneity will be considered statistically significant if the *P* value for Cochran's chi-square test is < 0.10.[59]

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

- 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 may be 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 may also be considered.

Publication Bias

If there are 10 or more included studies of a given study design and a particular outcome, publication bias will be assessed visually using funnel plots and objectively using Egger's regression test and Begg's rank correlation test.[60]

Reporting of Findings

The SR will be prepared in consideration of relevant reporting guidelines (i.e., PRISMA statement,[45] PRISMA harms,[61] and Meta-analysis Of Observational Studies in Epidemiology [MOOSE] reporting checklist[62]) and will meet the criteria outlined in A Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist.[63]

Economic Review

A primary economic analysis will be conducted to evaluate the long-term cost-effectiveness of MIGS devices and procedures from a Canadian public payer perspective to address the following research question:

Research Question 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?

Primary Economic Analysis

A decision analytic model will be developed to assess the costs and health outcomes associated with MIGS to treat glaucoma in adults.

The comparators considered will mirror those in the clinical review, including different MIGS, pharmacotherapy, laser therapy or invasive filtration surgeries. If data exist on MIGS procedures with cataract surgery, they will also be examined. Although the optimal sequence of therapy to treat glaucoma may be of interest, given that patients progress through the disease trajectory, there is unlikely to be clinical evidence to inform comparisons of sequences of treatment. Further attempts at considering this will exponentially increase the complexity of the economic model. As such, this analysis will evaluate single treatments as opposed to a sequence of treatment strategies. If available, the economic analysis will make specific considerations on different patient subgroups (e.g., severity of disease, treatment-naive or -experienced, previous surgical or medical treatment) to shed light on the relative cost-effectiveness of MIGS under these different patient subpopulations.

Model Design

The Markov cohort model will be based on published economic evaluations in glaucoma.[64,65] The model will evaluate, for different patient subgroups (e.g., treatment experience, disease severity), the cost-effectiveness of MIGS when compared with a set of clinically appropriate single interventions.

Markov states will reflect health states relevant to the natural history of glaucoma and the nature of the treatments being evaluated. These will include different disease severities, transitions to blindness (unilateral or bilateral) and death as above. Medical complications, as well as surgical complications from each procedure, will be accounted for in the model. The clinical and economic importance of each complication will be assessed by the clinical expert; those that are clinically meaningful will be incorporated into the model. Preliminary data indicate that IOP is the most commonly reported outcome from available trials, and is a reasonable surrogate to indicate the likelihood of future vision-related outcomes, including loss of vision. As such, a cost-effectiveness analysis using IOP as the effectiveness metric will be used.

Clinical experts and members of CADTH's Health Technology Expert Review Panel (HTERP) will be consulted as a means to ensure that the model structure reflects existing clinical literature and Canadian clinical practice. Checks on the internal and external validity of the model will be performed to assess for any logical discrepancies. The model will be created on TreeAge Pro Suite (Williamstown, Massachusetts).[66]

Perspective

The primary perspective will be that of a publicly funded health care system (i.e., a provincial ministry of health). A secondary societal perspective will also be presented to account for patient-borne costs (e.g., lost productivity due to blindness, etc.).

Resource Use and Cost Data

The costs captured will reflect the perspectives of the analysis. All costs will be reported in Canadian dollars and will be inflated to 2017 costs using the general consumer price index in Canada.[67]

The cost of each treatment strategy will be determined from focused literature searches and searches of Canadian cost sources (e.g., Canadian Institute for Health Information, National Ambulatory Care Reporting System, etc.), with preference given to Canadian data. If literature is lacking, other estimates of resource utilization will be sought from manufacturers of equipment and supplies; hospitals and clinics that deliver these treatment strategies; or from informed and guided expert opinion. Capital as well as ongoing costs will be accounted for; cost categories of interest include equipment, disposables, overhead, and labour. It will be assumed that treatment strategies will only be performed where there are reasonable economies of scale and volume-based analyses will not be conducted. A similar approach will be taken to estimate the cost of complications. Recognizing that these procedures may be conducted in the private or public health care system, actual cost versus charges will be assessed and actual cost to the public health care system will be used.

Physician fees will also be incorporated, recognizing that there may be alternative current or proposed approaches to physician reimbursement. Alternative approaches to physician reimbursement (and their potential to act as an incentive or disincentive toward various procedures) will be discussed.

Utilities

Utilities associated with each health state and the disutility of complications will be obtained from a focused literature search, and expert opinion may be used if the data are not available. Canadian sources will be preferred where available.

Clinical Parameters

The natural history and disease trajectory of patients with glaucoma will be based on existing literature. The systematic review conducted to address the clinical research question will support parameterization of the effectiveness and safety of the treatments under consideration in the economic analysis. The clinical review will provide data on the relative risk of important events including IOP and glaucoma severity and blindness, as well as type and frequency of complications.

Outcomes

The expected costs and quality-adjusted life-years (QALYs) associated with different treatment strategies, over the model's time horizon, will be estimated. QALYs will represent the main clinical outcome modelled as this single measure is multi-dimensional and can

capture the effect of the disease and its treatment on patients' morbidity and mortality. The primary economic outcome calculated will be the incremental cost-effectiveness ratios, measured in terms of the incremental costs per QALY gained.

Time Horizon and Discounting

As glaucoma is a progressive neuropathy that leads to irreversible loss of vision, a lifetime time horizon will be considered to account for all relevant clinical and cost consequences of treatment. Alternative time horizons may be assessed in the scenario analysis to evaluate the model's sensitivity to uncertainty from extrapolation. A discount rate of 1.5% will be applied to both costs and effects, with sensitivity analysis conducted across a range of discount rates (e.g., 0% and 5%).[68]

Sensitivity Analysis

All sources of uncertainty, as well as variability, will be identified and tested. The base-case analysis will represent the probabilistic findings, capturing the impact of parameter uncertainty on the cost-effectiveness results. If a cost-utility analysis is feasible, a cost-effectiveness acceptability curve will be generated to present the treatment strategies that form the efficiency frontier (i.e., the set of treatment strategies that produces the highest health benefits across different willingness-to-pay thresholds).

Uncertainty in the model will further be evaluated in a number of ways. Scenario and stratified subgroup probabilistic analysis will be performed to evaluate structural uncertainty and heterogeneity respectively. Potential subgroups of interest to the economic analysis that may be considered in stratified analyses include:

- Previous treatment experience: treatment-naive versus treatment-experienced
- Primary versus secondary glaucoma
- Open-angle versus angle-closure glaucoma
- Severity of glaucoma: early, moderate, advanced
- Number of eyes affected.

Other sensitivity analyses may be conducted in response to the findings of the other sections of the review.

Assumptions

During the course of the development of the economic model, assumptions and limitations will be identified and acknowledged in the written report. Where possible, assumptions will be tested through the conduct of appropriate sensitivity analyses.

Patient Perspectives and Experiences Review

Overview

Patient perspectives and experiences of glaucoma and MIGS will be incorporated in this review through two activities: a systematic review and thematic synthesis of qualitative studies; and patient engagement.

Review Study Design

A systematic review and qualitative synthesis of primary qualitative research describing the perspectives and experiences of patients with glaucoma and of their caregivers will be conducted. The results of included studies will be synthesized using thematic synthesis,[69] an approach that draws on methods for analysis from grounded theory and meta-ethnography.[70] Thematic synthesis is an interpretive approach that facilitates the development of both descriptive and interpretive findings that address the policy question of this HTA.

This protocol provides a general overview of the methods to be used at each stage of the study. Protocol refinement and amendment will be actively engaged at several stages as the review team responds to the set of eligible studies and available data for analysis. The potential for refinements and amendments are identified in each of the sections below. This iterative approach to protocol development and execution is not only consistent with the inductive principles of qualitative research, but also allows for further reflection on the relationship between the available qualitative studies and the decisions on study selection, data collection, extraction and analysis. Any subsequent refinements or amendments will be documented along with their rationale. The synthesis will be reported using Enhancing Transparency in Reporting the Synthesis of Qualitative Research (ENTREQ) guidelines for reporting qualitative research syntheses.[71] The review team will comprise three researchers, two of whom have experience and training in conducting both primary and secondary qualitative research, and another with experience in systematic reviews of qualitative research. This review will address the following research question:

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

Secondary Research Questions

Given the specificity of MIGS devices and procedures and their relatively new introduction into the course of care for patients with glaucoma, we expect to find few, if any, qualitative studies that report on the experiences and perceptions of patients who have had MIGS. To ensure the relevance of the analysis to the question of this review, a secondary set of research questions during data extraction and analysis will be explored:

A. How do patients experience and perceive their glaucoma and their prognosis?
B. How do patients experience and perceive treatment(s) for their glaucoma?
C. What are the ways in which glaucoma and its treatment affect patients' lives and the lives of their caregivers?

D. What do patients value or expect with regard to their treatment for glaucoma?

E. Are there differences in perceptions and experiences relating to glaucoma and its treatment among patients, or between patients and clinical and non-clinical caregivers?

F. What are health care providers' experiences and perceptions of caring for patients with glaucoma?

Appendix 6 (Figure 2) provides a visual mapping of the relationship between the primary and secondary questions. With the primary research question orienting the data selection, collection, and analysis toward patients' and caregivers' experiences and perceptions, the secondary research questions assist in interpreting findings to answer the question of this HTA. They have been crafted to reflect concepts relating to research questions from other sections of this HTA and will be used by the qualitative research team as sensitizing concepts (to orient the researchers' observations), and will be further refined, with possible additional questions added, during data collection and analysis.

Literature Search

The literature search will be performed by an information specialist, using a peer-reviewed search strategy. The search strategy for the patient perspectives and experiences review is presented in Appendix 3.

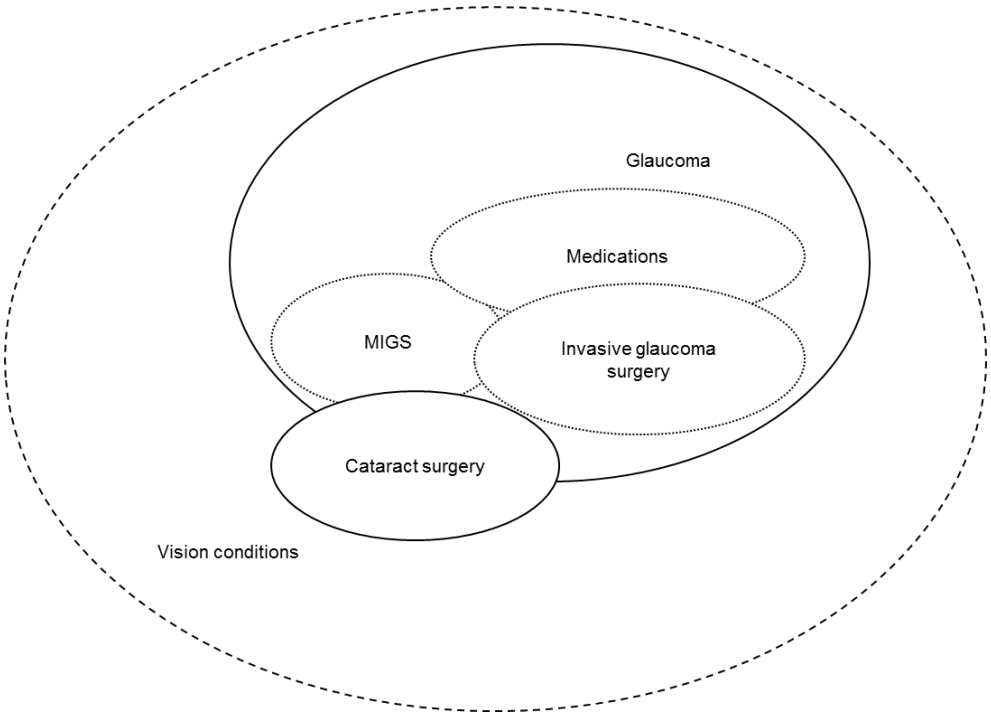
Information related to social dimensions will be identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates, CINAHL (1981–) via EBSCO, PubMed, and Scopus. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be glaucoma, minimally invasive glaucoma surgery, minimally invasive glaucoma surgical devices, and cataract removal surgery.

Methodological filters will be applied to limit retrieval to qualitative studies, including surveys or questionnaires, or studies relevant to patient perspectives. No date or language limit will be applied.

The initial searches will be completed in November 2017. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be 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 will be incorporated into the analysis of the final report. Any studies identified after the stakeholder feedback period will 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) will be 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 will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Figure 1: Possible modifications to expand and focus search for relevant qualitative studies



Reference lists of included studies and all qualitative syntheses retrieved (whether included or excluded) will be screened for any potential eligible studies.

Literature Selection Criteria

Inclusion Criteria

Eligible studies will be 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, qualitative studies are studies that 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). The qualitative component of mixed-method studies will be included. Studies that have multiple publications using the same data set will be included if they report on distinct research questions. Duplicate publications using the same data with the same findings will be excluded. Table 2 describes the eligibility criteria to be used, built using the Sample, Phenomenon of Interest, Design, Evaluation, Research (SPIDER) criteria for framing qualitative evidence synthesis research questions.[72]

Qualitative research can be difficult to find due to inconsistency in indexing terms and the challenges in retrieving qualitative studies using validated search filters.[73] In addition to the methods described above, the literature search may be modified and re-run depending on the set of studies that meet the inclusion criteria. During the completion of full-text review of eligible studies, the review team may conclude that the initial search did not include a term or concept seen in the literature that is relevant for inclusion, or that the number of included studies is likely to be small (< 20 studies). While it is possible to describe the results from a small set of studies, it is difficult to reorder and reimagine the perceptions, experiences, and themes reported to produce de novo analyses. In this case, the search may be redefined to either broaden it (e.g., include cataracts without glaucoma) or capture additional experiences or constructs of interest (e.g., living with blindness). Figure 1 illustrates the types of modifications that may be considered. The initial search will be for the concepts contained within the solid lines, i.e., glaucoma and cataract surgery, separately. We anticipate that this search will retrieve additional studies addressing the concepts in the dotted lines. Should the team determine that it is necessary to expand the literature search to capture an additional set of studies, it may expand the search to probe vision conditions more generally (the dashed line). This decision will be made by consensus by the review team and the decision will be documented.

Table 2: Eligibility Criteria

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

There is no standard approach to including primary studies and syntheses in a qualitative synthesis. Typically, in quantitative syntheses, only primary studies will be included to avoid the issue of "double counting" or giving undue weight to one set of study findings. Following these principles, and based on full-text reviews of study methods and findings, only qualitative syntheses that provide novel interpretations of existing data will be included. Studies with findings that are aggregative and descriptive will be excluded. However, to produce a de novo interpretive analysis — and once the analysis is nearly complete and after theoretical saturation is confirmed — data from syntheses will be analyzed using syntheses to triangulate the findings with those additionally in the literature.

All studies regardless of comparability of health care systems will be included; considerations of transferability (i.e., external validity) will be raised during data extraction, critical appraisal, and analysis.

Exclusion Criteria

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

Literature Screening and Selection

Title and abstract screening will involve two reviewers experienced with qualitative syntheses independently assessing titles and abstracts of potentially eligible studies in DistillerSR.[74]. Disagreements about eligibility at the title and abstract level will be resolved through discussion, with a third reviewer if required.

The same two reviewers will conduct full-text screening and independently assess studies for inclusion. Again, differing judgments about study inclusion will be resolved through consensus. Study selection will be documented and reported using a PRISMA flow diagram.[45]

At this stage, the team will review the set of included studies and discuss whether the final set of studies includes sufficient data for analysis or if there is need to modify the literature search and selection criteria. Reflection on the potential need to refine primary and

secondary research questions will occur should modifications to literature search and selection criteria be necessary.

Data Extraction

One reviewer will extract data describing study and sample characteristics for each study using electronic data extraction forms (see Appendix 8 for draft versions of the Table of Included Studies and Table of Sample Characteristics), with a second reviewer checking data extraction. Data extraction will begin by testing these forms with both reviewers extracting information from a small sample of studies (approximately six) to ensure that they facilitate the consistent extraction of study and sample details that are informative for this review. Modifications to the data extraction forms will be made based on the reviewers discussing the extraction process and identifying possible differences in interpreting fields and information contained in studies not captured by the existing form.

Quality Assessment

Two reviewers will independently critically appraise all included studies concurrently with data extraction and checking. The 10 items of the Critical Appraisal Skills Program Qualitative Checklist[75] will be used as prompts to guide the critical appraisal. Reviewers will independently document their assessments on the major strengths and limitations of studies in terms of credibility, transferability, dependability, and confirmability[76] using a Table of Quality Appraisal (Appendix 8). Disagreements in assessments will be resolved through discussion, involving a third reviewer if required.

There is no consensus on how qualitative syntheses can integrate critical appraisals into the analysis. However, the general approach is to not exclude studies on the basis of quality assessments.[77] To use the critical appraisal to inform this review, the review team will reflect on key issues that appear in each domain (i.e., credibility, transferability, dependability, and confirmability). Studies that lack credibility (i.e., internal validity) or dependability (i.e., reliability) may be coded last so they do not drive the analysis once the coding structure is built. Similarly, the transferability of findings during the analysis and reporting results will be considered. As this approach will be constructed while conducting the review, decisions and processes with regards to integrating the results of the critical appraisal to make this approach transparent will be documented.

Certainty in the Evidence

GRADE CERQual (Confidence in Evidence from Reviews of Qualitative research) will be used to assess the overall confidence in each of the key findings.[78] Key research findings are the set of key themes, concepts, or perceptions or experiences identified as having the most relevance to the policy question. They will be selected through discussion among members of the review team, who will additionally consult with the section leads from Patient Engagement, Implementation, and Ethics.

Two reviewers will complete a CERQual Evidence table[78] to independently assess their confidence in each of the key findings based on four domains: methodological limitations, adequacy of the data, relevance and coherence. Similar to the approached used by GRADE, findings are initially assessed as high confidence, and then downgraded according to the limitations in each of the four domains, going from moderate confidence to low

confidence to very low confidence. Disagreements in judgment will be resolved through consensus, and recorded in a CERQual Summary of Qualitative Findings table[78] to facilitate overall judgments about confidence and transparency in study findings.

Data Analysis

NVivo 11[79] will be used to extract and manage qualitative data from included studies. Appropriate sections of the publication's findings will be coded (i.e., not background and discussion sections) to ensure the capture of qualitative data and findings (and not findings or interpretations of background literature or authors' conclusions).

The analysis will follow the principles of thematic synthesis, which draws on meta-ethnography and grounded theory.[70] Three-stage formal coding procedures are central to thematic synthesis and facilitate (in conjunction with using qualitative data analysis software) the reordering, selection, and interpretation of data, codes, their connections and contexts, which supports the development of descriptive (second-stage coding) and analytic (third-stage coding) findings. The three stages of coding that will be passed through are open or line-by-line coding, descriptive coding, and developing analytic themes.[80] These coding practices draw heavily from grounded theory, with the addition of the "reciprocal translation" concept from meta-ethnography, in which, in the first and second stage of coding, the act of coding and sorting "like with like" is part of translating findings across studies.[70,81]

Thematic synthesis borrows the constant comparison method from grounded theory and will be practised by comparing codes across reviewers, codes across codes, and codes across studies.

Two reviewers will independently conduct line-by-line coding of an initial set of four to six studies. Line-by-line coding encourages "staying close to the data," a process that encourages the inductive development of codes. Upon completing this initial set, the review team will meet to discuss and reflect on the coding process, and a decision will be made to either continue line-by-line coding or move toward developing descriptive codes. Further line-by-line coding will be warranted if no patterns appear in the open codes used and if each passage being coded continues to give rise to a new set of codes (i.e., there is no stability in the codes being used). In this case, the two reviewers will return to the data, repeat the process of line-by-line coding of a subset of studies (approximately four), and meet again to review their experiences of the coding process.

Once reviewers decide that the line-by-line coding is sufficient (i.e., patterns have emerged in the codes used), they will begin descriptive coding. Two reviewers will use the secondary research questions as guides and begin to develop and refine a set of descriptive codes by coding a subset of studies (approximately five or fewer). During this period of descriptive coding, reviewers will use larger passages of text to group and cluster codes using descriptive concepts that remain close to the data. Upon completing this subset, the reviewers will meet and discuss the coding process and reflect on the breadth of descriptive codes and their related concepts as part of refining the coding set. Once the reviewers have come to a consensus about a set of codes that describe the dimensions of the data relevant to the primary and secondary research questions, the primary coder will code the remaining studies. This descriptive coding remains close to the data, describing "second-order interpretations" that are consistent with reciprocal translation.[70,81]

The second reviewer will continue to verify descriptive codes through a review of codes and their structure and through coding data. The reviewers will compare and contrast their descriptive codes with each other and across the studies. The review team will hold frequent meetings to discuss coding structure and data interpretation and to encourage reflection on the relationship between descriptive codes and the secondary research questions. Coding is an iterative process, and as new codes emerge inductively, the primary reviewer will recode already-coded studies to identify all instances of the concept. As the descriptive codes become hierarchical (i.e., the review team is able to identify higher-order constructs or categories for which descriptive codes are dimensions or facets) and the relationship between codes becomes the subject of the analysis, the team will move from descriptive coding to analytic synthesis.

Analytic synthesis is the development of themes or abstracted constructs that are interpretations of the data. To develop analytic themes, memoranda and diagrams will be used to assemble and sort the previously established descriptive codes, going back to the data to further develop the relationship between themes and codes. In keeping with the iterative nature of qualitative analysis, the reviewers may revert to descriptive coding to describe additional dimensions or facets of particular codes or themes to develop themes that are conceptually rich (described in rich detail and clearly supported by data). The purpose of this third stage of coding is interpretation — to produce something beyond the description of results. Further, to ensure that findings attend to the variety and richness of the primary research, variation across and within characteristics, including quality appraisal, will be explored. This analytical approach ensures that the review is more than a summary of findings of qualitative studies, but rather a new synthesis or interpretation of the existing published data in relation to the policy question.

Preliminary findings will be presented to stakeholders, including a patient representative, for input. This will be done to explore whether the analysis is supported by the data and if there are known themes in the literature or delivery landscape not adequately accounted for in the analysis. Taking these perspectives into account, the review team will return to the data and refine the analysis accordingly. At this point, any included qualitative synthesis will be analyzed and the findings compared and contrasted with the preliminary analysis. Triangulating this analysis with other syntheses and exploring reasons for differences and similarities will strengthen the analysis by accounting for divergent cases. Analytical synthesis will stop once themes (findings) and their relationships have been richly described and are stable, with no additional descriptive or interpretive insights arising from further analysis.

Data that are relevant to the questions of this review but do not feature prominently in the data set will be coded and analyzed even if there is an absence of theoretical saturation around those codes and they remain descriptive rather than analytic. Similarly, in an effort to ensure the findings are relevant to the concrete policy questions under consideration, and where applicable, the analysis will be conducted for overall patient experience and by technology and subpopulations. Exploring concepts and themes that may apply uniquely or particularly to certain types of treatment (e.g., medications, laser surgeries) or subpopulations (e.g., elderly persons > 80 years of age) will help inform decision-making.

Reflexivity is a epistemological principle and methodological approach in qualitative research that recognizes the role of the researcher as an instrument. Reflexive practices and techniques are those that allow for and facilitate making researcher's observations and

interpretations transparent and explicit rather than implicit and unacknowledged. They aim to provide cognitive and emotional space to separate researchers from the act of analysis and allow them to reflect on the act of observation and interpretation itself. This study employs the reflexive practices of memoing and frequent dialogue among team members to probe and position reviewers in relation to the analysis. Further, the review team will proactively search for possible alternative interpretations of the analytic findings and triangulate them with additional empirical sources and patient engagement to identify observations and alternative interpretations that otherwise might be ignored.

Techniques to Strengthen Methodological Rigour

In addition to the methods described above, the credibility of the analysis will be strengthened by comparing and contrasting findings with existing published qualitative and quantitative studies on patient experiences and perspectives on glaucoma and its treatment. Further, the review team will engage several patients with glaucoma and/or glaucoma and MIGS at several stages of this review, as detailed in the Patient Engagement section.

Patient Engagement

This protocol outlines how CADTH will engage patients who have glaucoma with or without experience of MIGS in interviews and discussion to inform the development of the study protocol and research questions, the interpretation of findings of the patient perspectives and experiences section, and reporting of study results. We describe how patient engagement is to be used in the assessment, to be accountable to the people we engage.

Methods of Engagement

Invitation to Participate

We will engage three adults aged 18 years and older with glaucoma and with or without experience of MIGS. Potential participants will be identified through multiple sources including but not limited to: patient organizations including the Glaucoma Research Society of Canada, Patients4Change, Foundation Fighting Blindness, Canadian Council of the Blind, and Canadian National Institute for the Blind; clinical experts involved in the project; CADTH liaison officers; and other CADTH networks across Canada. A CADTH Patient Engagement Officer will contact potential participants by phone or email to explore their interest in becoming involved. The preliminary request will describe CADTH and the purpose and scope of this HTA, the purpose of engagement and the nature of engagement activities, and invite the person to participate in the project. Should they be interested in participating, we will obtain their informed consent.

Engagement Activities

Engagement activities will involve participants at several points during the assessment including:

- prior to protocol finalization
- during drafting of the final report
- upon project completion.

If consent is obtained, individual participants will then be led in conversation around their health condition and their treatment experiences and perspectives on those experiences. Additionally, key concepts identified by the assessment team through prior scoping activities will be explored, for example, challenges and barriers to the effective use of eye drops. Notes from the interview will be summarized, with any personal identifiers removed, and provided to individual participants for their review and edits, to ensure clarity and accuracy in representation of their experiences and perceptions. Revisions will continue until participants agree that the statements reflect the tenor and topics of the conversation.

Prior to protocol finalization, summaries of participant interviews were shared with the full assessment team and with members of CADTH's HTERP as appropriate to inform the project scope and selection of methods.

The next stage of engagement will occur once preliminary findings from the qualitative synthesis of patients' perspectives and experiences are available. At this time, individual participants will again be invited to be interviewed. The conversation will explore participants' perceptions of key findings, including if the findings are understandable, and if they reflect their experiences or understandings. These conversations will be used to consider the possible need to explore avenues of analysis that have been missed or underdeveloped, add additional concepts or experiences that relate to identified categories, or inform the processes underlying glaucoma treatment and the context of analysis.

Final conversations will be had with participants upon completion of the assessment and HTERP deliberation and recommendation development. Through conversation we will share the key results of the full assessment, including the HTERP recommendation document, and describe how engagement activities were used.

Reporting

Throughout the assessment process and during team meetings, we will take detailed notes so as to outline in a final report the process of engagement and where and how participants' contributions were used in the assessment.

Ethics Analysis

The purpose of this analysis is to identify and reflect on 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 broadly ethical concerns, the aim of this analysis is to make such issues explicit and 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 ELSI (ethical, legal, and social issues) when addressing broader values-related considerations. While the primary emphasis here will be on ethical considerations, legal and social issues may also figure in the discussion. For example, we know that in the case of other clinical conditions and screening programs (e.g., colon cancer screening) that patients' social class is correlated with which forms of medical intervention are considered most appropriate by physicians and adopted by patients. In this HTA it will be necessary to consider a potential new intervention for adult glaucoma in light of such phenomena.

There are two sets of questions to consider when comparing MIGS with pharmaceutical management and filtration surgery. The ethics analysis will address 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?

Inquiry

Bioethical analysis requires a two-step approach to identifying potential issues. The first is a review of the ethics, clinical, and public health literatures to identify existing ethical analyses of the technology. The second is a novel ethical analysis based on gaps identified in the ethics literature and the results of concurrent reviews. This may require selective searches to provide a basis in theoretical ethics, in applied ethical analyses of similar technologies, and in evidence for the ethical analysis of emerging issues specific to MIGS and pharmaceutical management of glaucoma. By this approach, we will identify and assess the relative importance and strength of the identified concerns and proposed solutions, identify and assess issues that have not yet come to the attention of ethics researchers, and delineate ethical desiderata for possible solutions to the issues for which such solutions have not yet been proposed.

Insofar as this process involves ethical concerns in applied ethics, typically the analysis will reflect on the specific details of community and patient perspectives, clinical effectiveness and safety, economic analysis, environmental impacts, and implementation considerations. As such, the ethical review involves an iterative process whereby the analysis is responsive to results emerging from clinical, implementation, patient perspective, and economic reviews.

Literature Search

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

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

Methodological filters will be 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 will be limited to English- or French-language publications.

The initial searches were completed by November 2017. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be 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 will be incorporated into the analysis of the final report.. Any studies that are identified after the stakeholder feedback period will be 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) will be 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 will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Review of the Bioethics Literature

A review of the empirical and normative bioethics literature will be conducted to identify literature relevant to the identification and analysis of the potential ELSI issues related to the use of MIGS

Literature Selection Criteria

We will search for articles, studies, and reports that explicitly and specifically raise 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.

Literature Screening and Selection

The selection of relevant literature will proceed in two stages. In the first stage, the title and abstracts of citations will be screened for relevance by a single reviewer. Articles will be categorized as "retrieve" or "do not retrieve," according to the following criteria:

- Provides normative analysis of an ethical issue arising in the use of MIGS or pharmaceutical management of glaucoma
- Presents empirical research directly addressing an ethical issue arising in the use of MIGS or pharmaceutical management of glaucoma
- Explicitly identifies but does 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 will be reviewed by a single reviewer. Reports meeting the above criteria will be included in the analysis, and reports that do not meet these criteria will be excluded.

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.

Data Extraction and/or Abstraction Strategy

The bibliographic details for each report (author, publication date, journal), the potential ethical issues raised, and the report's conclusions (issues identified, values at stake identified through normative analysis, and solutions proposed, and their normative justification if presented) will be summarized in a table.

Analysis

The ethical issues identified, values described, and solutions proposed in the literature at this stage will be evaluated using the methods of ethical (applied philosophical) analysis, which includes: applying standards of logical consistency and rigour in argumentation, particularly where specific implications are identified and specific solutions advocated; responsiveness to important values of health care and health care policy in the field in which the technology is proposed for implementation; relevance to the context for which the technology is being considered; and the representation of perspectives from diverse relevant communities, particularly attending to the possibility of the neglect of marginalized and vulnerable populations.

The proposed analysis will draw most directly on two classic perspectives that are well established in the health ethics literature, namely the utilitarian/consequentialist approach and the deontological/duty-based approach. The former focuses more directly on the overall consequences of a particular course of action and deals with questions of individual rights and duties and considerations of social justice only indirectly. Conversely, the deontological approach gives priority to considerations of individual rights and concomitant duties while treating overall utility (i.e., the greatest good for the greatest number) as of only secondary

importance. From a deontological perspective the most important consequence to consider is whether individual rights are properly honoured and accounted for irrespective of whether some supposedly greater good might be accomplished by ignoring the rights of certain individuals. While these two theoretical approaches are often treated as opposed, there is a well-established tradition within contemporary health care ethics that treats them as complementary. Depending on the nature of the issue and the context in which it arises, it is possible that other normative ethical perspectives may be invoked in the analysis (e.g., virtue theory may be particularly relevant to issues regarding professional conduct of ophthalmologists).

Summarizing and Presenting Results

The reporting of ethical issues will follow the key values identified or issues being explored and will be determined by the values and issues that are identified. For example, the results may be summarized according to a principlist framework (issues concerned with autonomy, beneficence, non-maleficence, and justice) or by categorizing moral concerns as micro-, meso-, and macro-level issues. Regardless of the framework selected, the implications of the choice of framework on how the findings are presented and interpreted will be described. In addition, where the report undertakes analysis that is not derived from the peer-reviewed literature, this will be noted in the interests of transparency.

Ethical analysis assists in social and policy decision-making but is not itself the basis for legitimate social decision-making, which requires consultation with and deliberation by relevant stakeholders in a given context. Decisions will also be sensitive to emerging empirical evidence. Furthermore, the ethical implications of a health technology are often determined by the nature of the local context. The implications of values of fair access and consistency of service within the population, for example, are determined by facts about how health care services are arranged and provided.

Given these features of ethical decision-making, results of the ethics review will be presented in a way that helps decision-makers better understand the ethical implications of their decisions and recommendations they make. For example, a number of contextualizing questions will be developed based on the identified issues so that decision-makers can assess localized impacts, and proposed solutions will be analyzed to indicate the relevant ethical trade-offs at stake and mitigation strategies that could be employed to manage these trade-offs.

Implementation Issues Analysis

To help inform the decision regarding the optimal use of MIGS procedures in Canada for adult patients with glaucoma, the following implementation question will be addressed:

Research Question 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?

The implementation issues analysis will identify implementation considerations associated with MIGS procedures available in Canada for the treatment of adults with glaucoma. The analysis will also identify relevant factors that need to be considered in urban, rural, and remote settings across Canada with respect to implementation of MIGS procedures.

Methods

To understand implementation issues associated with implementing MIGS procedures in Canada, a dual-stage research protocol will be followed. Findings from one stage will help inform the need and scope of the other stage of research. The two stages are consultations with key stakeholders and a review of the published literature.

Data Collection

Stage 1: Consultations

Consultations will be conducted with targeted experts and stakeholders identified through the clinician networks accessible to CADTH's knowledge mobilization team to provide a general overview of policy, practice, and issues related to the treatment of glaucoma using MIGS procedures as well as specific literature that may be important to incorporate. These stakeholders may include ophthalmologists and specialist surgeons, hospital administrators, researchers, or clinical decision-makers. Ophthalmologists from each province will be approached, including both physicians who currently perform MIGS procedures and those who do not or are working in provinces that are considering introducing the technology. Stakeholders from the other relevant groups listed will be approached and the number interviewed may change depending on the information provided or still lacking.

To guide the consultations, a semi-structured interview guide will be developed and interview questions related to implementation will be developed based on research questions and the type of expert being consulted. Consultations will be conducted by phone by a CADTH knowledge mobilization officer, and follow-up questions or clarifications will be conducted by email. Consent to publish comments and names, if needed, will be sought.

Stage 2: Literature Search

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

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

Methodological filters will be applied to limit retrieval to studies relevant to implementation issues. Retrieval will be limited to documents added to the databases since January 1, 2000. The search will be limited to English- or French-language publications.

The initial searches were completed in November 2017. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be 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 will be incorporated into the analysis of the final report. Any studies that are identified after the stakeholder feedback period will 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) will be 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, 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 will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Eligibility Criteria

English-language reports that describe implementation and context issues, including challenges and enablers, associated with treating glaucoma using MIGS procedures will be included.

Screening and Selecting Articles for Inclusion

Articles will be screened and selected for inclusion based on the described eligibility criteria by one reviewer. First, titles and abstracts will be reviewed to identify potentially papers; then the full text of all potentially relevant reports will be retrieved for definitive determination of eligibility.

Data Extraction

Data extraction will be performed by one reviewer. The data extracted will include bibliographic details of included papers, reported implementation challenges and enablers, and other key findings related to implementation and relevant context information.

Data Analysis

The analysis of data collected from each of the data sources (i.e., consultations and literature review) will be similarly guided, as below.

Perspectives

When analyzing data, the items coded and summaries written will be those most relevant at the health services delivery level. The aim will be to provide information to policy-makers regarding relevant contextual factors that influence the use of MIGS procedures in the treatment of adults with glaucoma.

Descriptive Analysis

The findings will be presented in a narrative summary. If possible, the summary will categorize findings based on INTEGRATE-HTA categories.[82] INTEGRATE-HTA defines eight domains of context (setting, geographical, epidemiological, socioeconomic, sociocultural, political, legal, and ethical) and four domains of implementation (provider, organization and structure, funding, and policy), each contributing differently to how an intervention is implemented, who can access it, and ultimately the effectiveness of an intervention. CADTH will add a patient domain under the implementation category.

Given the emergent nature of this topic area, the planned analysis could be revised based on the collected data.

A list and description of factors that have the potential to enable or create challenges to successful implementation will be presented, as well as a summary of potential strategies that could be used to implement or increase the uptake of the technology, if the decision is made to do so. Additionally, a summary of how each factor influences implementation will be provided and, where possible, strategies will be identified that could be used to ensure these factors are taken into consideration or mitigated.

Knowledge Mobilization

The implementation issues identified will guide the development of knowledge mobilization activities, tools, and tactics to support the implementation of any resulting decisions or changes to the health care system or health service delivery.

Protocol Amendments

If amendments to the protocol are required at any time during the study, reasons for changes will be recorded and reported in the final report.

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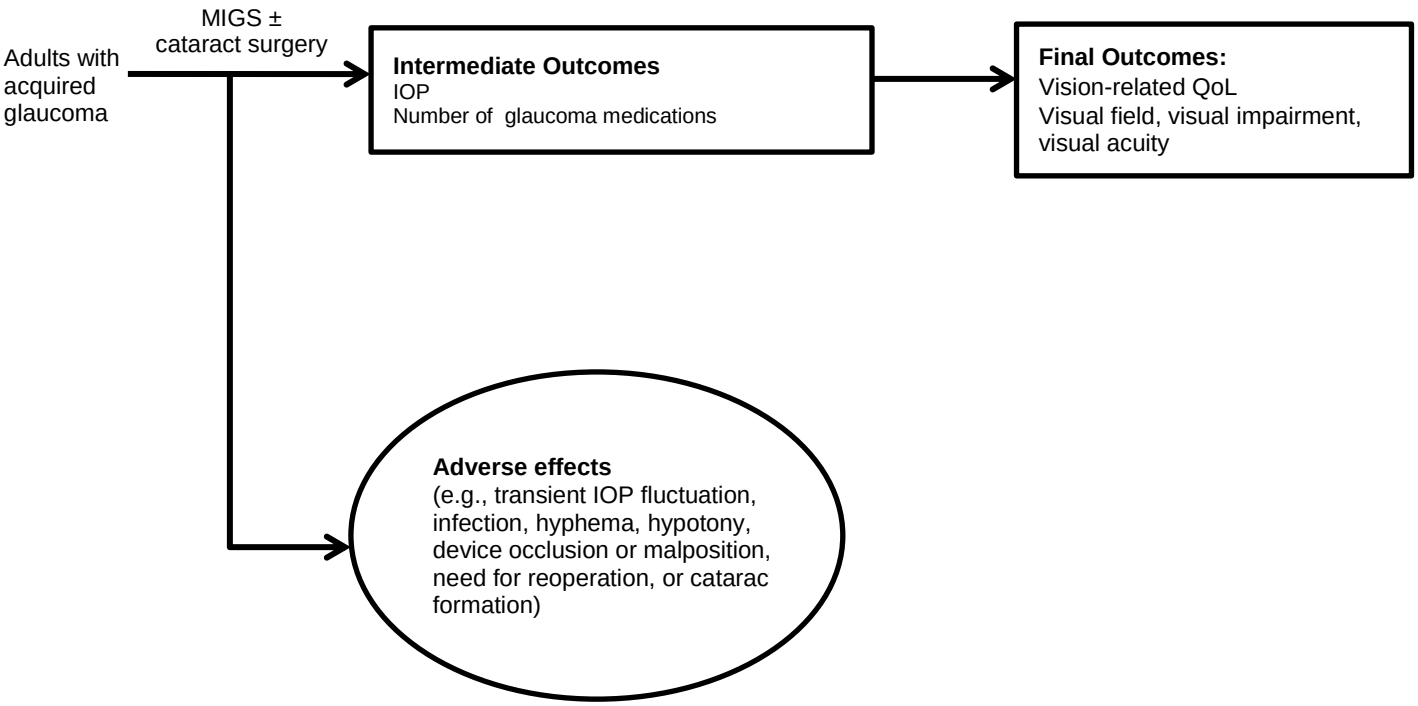
Appendix 1: MIGS Devices and Procedures of Interest

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.[13,15]
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.[13,24,83]
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.[84]
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.[13,20,24,31] Single or multiple iStents may be implanted.[24]
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.[23] The iStent Inject is preloaded with two stents, such that both can be placed without removing the injector from the eye.[23]
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).[36,84]
Approach: Increasing uveoscleral outflow via suprachoroidal shunts	
CyPass Micro-Stent	The CyPass Micro-Stent is a polyamide tube, 6.35 mm long with a 300 mm lumen,[85] that is implanted into the supraciliary space (between the ciliary body and the sclera)[85] to create a permanent channel between the anterior chamber and the suprachoroidal space.[13,86]
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,[85] measures 6 mm in length, and is available in three different options denoted by inner diameters of 45 µm, 63 µm, and 140 µm.[13,87,88] However, the manufacturer recommends only the 45 µm size to prevent hypotony.[85] The procedure may be augmented with subconjunctival injection of mitomycin-C to reduce scarring.[85]

ECP = endoscopic cyclophotocoagulation or endocyclophotocoagulation; GATT = gonioscopy-assisted transluminal trabeculotomy; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; TM = trabecular meshwork.

Appendix 2: Analytical Framework



IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; QoL = quality of life.

Appendix 3: Literature Search Strategy

Clinical Review Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to Present Ovid MEDLINE(R) ALL 1946 to present. **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	TBD
Alerts:	Monthly search updates until project completion.
Study Types:	No filters used
Limits:	Publication years 2000 forward English or French language Humans Conference abstracts removed

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 .dv	Publication type Device name (Embase)
medall	Ovid database code; Ovid MEDLINE(R) ALL 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Clinical Review Database Search**
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 ophthalmol*).jw.
5	1 or 2 or 3 or 4
6	exp Microsurgery/ or exp Minimally Invasive Surgical Procedures/ or stents/
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 medall
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 ophthalmol*).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	(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.
26	(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.
27	MIGS.ti,ab,kw,dv.
28	(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.
29	((Gonioscopy adj5 Trabeculotomy) or GATT).ti,ab,kw,dv.
30	(Excimer adj5 laser adj5 trabeculotom*).ti,ab,kw,dv.
31	(Endocyclophotocoagulation* or (Cyclophotocoagulation adj5 endoscop*)).ti,ab,kw,dv.

MULTI-DATABASE STRATEGY	
#	**Clinical Review Database Search**
32	Endoscope-assisted goniosynechialysis.ti,ab,kw,dv.
33	((Minimal* or Minimiz* or minimis* or micro*) adj5 (incision* or invasive* or penetrat* or surgery or surgeries)).ti,ab,kw.
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	exp Glaucoma/ or exp Glaucoma Drainage Implants/ or exp Sclerostomy/ or exp Trabeculectomy/
38	(glaucoma* or antiglaucoma*).ti,ab,kf.
39	((open or close or closed or OAG or CAG or POAG or COAG) adj5 angle* adj5 (eye or eyes or ocular*)).ti,ab,kf.
40	(glaucoma* or ophthalmol*).jw.
41	37 or 38 or 39 or 40
42	exp Microsurgery/ or exp Minimally Invasive Surgical Procedures/ or stents/
43	((Minimal* or Minimiz* or minimis* or micro*) adj5 (incision* or invasive* or penetrat* or surgery or surgeries)).ti,ab,kf.
44	(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.
45	(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.
46	MIGS.ti,ab,kf.
47	(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.
48	((Gonioscopy adj5 Trabeculotomy) or GATT).ti,ab,kf.
49	(Excimer adj5 laser adj5 trabeculotom*).ti,ab,kf.
50	(Endocyclophotocoagulation* or (Cyclophotocoagulation adj5 endoscop*)).ti,ab,kf.
51	Endoscope-assisted goniosynechialysis.ti,ab,kf.
52	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53	41 and 52
54	53 use cctr
55	18 or 36 or 54
56	exp animals/
57	exp animal experimentation/ or exp animal experiment/
58	exp models animal/
59	nonhuman/
60	exp vertebrate/ or exp vertebrates/
61	or/56-60
62	exp humans/
63	exp human experimentation/ or exp human experiment/
64	or/62-63

MULTI-DATABASE STRATEGY	
#	**Clinical Review Database Search**
65	61 not 64
66	55 not 65
67	66 not conference abstract.pt.
68	limit 67 to yr="2000 -Current"
69	limit 68 to english language
70	68 and french.lg.
71	69 or 70
72	remove duplicates from 71

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.
Cochran 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.

Patient Perspectives and Experiences Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE(R) ALL 1946 to present
Date of Search:	TBD
Alerts:	Monthly search updates until project completion.
Study Types:	Qualitative studies, including surveys and questionnaires
Limits:	No limits

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)
.pt	Publication type

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experiences Database Search**
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.

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experiences Database Search**
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.
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.

MULTI-DATABASE STRATEGY	
#	**Patient Perspectives and Experiences Database Search**
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
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.
CINAHL (EBSCO interface) Scopus	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform. Same keywords, and date limits used as per MEDLINE search. Syntax adjusted for Scopus platform.

Grey Literature

Dates for Search:	TBD
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)
- Clinical Trial Registries
- Internet Search.

CADTH

Appendix 4: Screening Checklist – Clinical Review

Level 1: Title and Abstract Screening

Reviewer: _____ Date: _____

Ref ID: **Author:** **Publication Year:**			
Did the study include:	**Yes (Include)**	**Unclear (Include)[a]**	**No (Exclude)**
1) The population of interest: *≥ 80% of the sample contains:* Adults (mean age of ≥ 18 years) with acquired glaucoma NOT: juvenile/congenital glaucoma, ocular hypertension, or animal or ex vivo populations	☐	☐	☐
2) The intervention of interest: Any of the following MIGS, performed *with or without* cataract surgery (i.e., phacoemulsification): • ECP • Trabectome • Kahook Dual Blade • iStent (first generation) • iStent Inject (second generation) • iStent Supra (third generation) • CyPass Micro-Stent • GATT • XEN 45 Gel Stent • XEN 63 Gel Stent • XEN 140 Gel Stent	☐	☐	☐
3) A comparator of interest: Any of the following: • Alternative 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) • Alternative MIGS device or procedure performed in combination with cataract surgery (i.e., phacoemulsification) • Cataract surgery (i.e., phacoemulsification) alone	☐	☐	☐
4) Outcome(s) of interest: • IOP • Number of glaucoma medications used • Vision-related QoL • Adverse events and complications (e.g., transient IOP fluctuation, infection, hyphema, hypotony, device occlusion or malposition, need for reoperation, or cataract formation)	☐	☐	☐
5) A study design of interest:	☐	☐	☐

• RCTs • Non-randomized controlled trials • Cohort studies • Case-control studies NOT: • Case reports • Case series • Review articles • Editorials, letters, commentaries • Conference abstracts or presentations • Thesis documents			
Notes:			
Decision for including the record at level 1:[b]	**Yes** ☐	**No** ☐	

ECP = endoscopic cyclophotocoagulation or endocyclophotocoagulation; GATT = gonioscopy-assisted transluminal trabeculotomy; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; QoL = quality of life; RCT = randomized controlled trial.
[a] "Unclear" signifies that the relevant information cannot be ascertained from the title and abstract.
[b] If all items above are answered yes or unclear by at least one of two independent reviewers, then the full text will be retrieved for further review.

Level 2: Full-Text Screening

Reviewer: _____ Date: _____

Ref ID: **Author:** **Publication Year:**		
Did the study include:	**Yes (Include)**	**No (Exclude)**
1) The population of interest: ≥ *80% of the sample contains:* Adults (mean age of ≥ 18 years) with acquired glaucoma NOT: juvenile/congenital glaucoma, ocular hypertension, or animal or ex vivo populations	☐	☐
2) The intervention of interest: Any of the following MIGS, performed *with or without* cataract surgery (i.e., phacoemulsification): • ECP • Trabectome • Kahook Dual Blade • iStent (first generation) • iStent Inject (second generation) • CyPass Micro-Stent • GATT • XEN 45 Gel Stent • XEN 63 Gel Stent • XEN 140 Gel Stent	☐	☐
3) A comparator of interest: Any of the following: • Alternative MIGS device or procedure • Pharmacotherapy alone • Laser therapy (e.g., excimer laser trabeculotomy, selective laser trabeculoplasty) • Filtration surgery (e.g., trabeculectomy or aqueous shunt implantation) • Alternative MIGS device or procedure performed in combination with cataract surgery (i.e., phacoemulsification) • Cataract surgery (i.e., phacoemulsification) alone	☐	☐
4) Outcome(s) of interest: • IOP • Number of glaucoma medications used • Vision-related QoL • Adverse events and complications (e.g., transient IOP fluctuation, infection, hyphema, hypotony, device occlusion or malposition, need for additional procedures, or cataract formation)	☐	☐
5) A study design of interest: • RCTs • Non-randomized controlled trials • Cohort studies • Case-control studies	☐	☐

NOT: • Case reports • Case series • Review articles • Editorials, letters, commentaries • Conference abstracts or presentations • Thesis documents		
Notes:		
Decision for including the record at level 2:[a]	**Yes** ☐	**No** ☐
Reason(s) for exclusion:	☐ Irrelevant population ☐ Irrelevant intervention ☐ Irrelevant comparator ☐ Irrelevant outcomes ☐ Irrelevant study design ☐ Other (specify):	

ECP = endoscopic cyclophotocoagulation or endocyclophotocoagulation; GATT = gonioscopy-assisted transluminal trabeculotomy; IOP = intraocular pressure; MIGS = minimally invasive glaucoma surgery; QoL = quality of life; RCT = randomized controlled trial.
[a] Both reviewers must answer "yes" to all questions for inclusion at the full-text level. If there is discrepancy between reviewers, conflicts will be resolved by discussion or with involvement of a third reviewer if necessary.

CADTH

Appendix 5: Clinical Review Data Extraction Form

Reviewer: _____ Date: _____

STUDY CHARACTERISTICS	
Ref ID:	
Author(s):	
Publication year:	
Publication title:	
Country (where the study was conducted, or the country of the corresponding author's affiliation):	
Funding sources:	
Study is relevant for clinical research question(s):	☐ 1 ☐ 2 ☐ 3 ☐ 4

METHODOLOGY	
Study design:	☐ RCT ☐ Non-randomized controlled trial ☐ Cohort study ☐ Case-control study
Study objectives:	
Inclusion criteria:	
Exclusion criteria:	
Recruitment method:	
Description of primary and secondary outcomes reported:	
Description of subgroup analyses of interest:	

RCT = randomized controlled trial.

POPULATION – OVERALL		
Number of patients/eyes:	Patients, N = ___	Eyes, N = ___
Age:		
Sex/Gender:		
Race:		
Type of glaucoma:	☐ Primary open-angle glaucoma ☐ Secondary open-angle glaucoma ☐ Angle-closure glaucoma ☐ Pigmentary glaucoma ☐ Pseudoexfoliation glaucoma ☐ Steroid-induced glaucoma ☐ Uveitic glaucoma ☐ Neovascular glaucoma ☐ Traumatic glaucoma ☐ Inflammatory glaucoma ☐ Refractory glaucoma	

POPULATION – OVERALL (continued)		
Type of eyes:	☐ Phakic ☐ Pseudophakic	
Glaucoma severity or stage:		
Baseline Characteristics		
IOP (mm Hg):		
Number of glaucoma medications:		
Treatment-naive or treatment-experienced (specify):	☐ Treatment-naive ☐ Current/previous pharmacotherapy: _____ ☐ Previous laser therapy: _____ ☐ Previous MIGS: _____ ☐ Previous filtration surgery: _____	
Relevant comorbidities (e.g., cataract):		
POPULATION – Intervention Group		
Number of patients / eyes:	Patients, n = ___	Eyes, n = ___
Age:		
Sex/Gender:		
Race:		
Type of glaucoma:	☐ Primary open-angle glaucoma ☐ Secondary open-angle glaucoma ☐ Angle-closure glaucoma ☐ Pigmentary glaucoma ☐ Pseudoexfoliation glaucoma ☐ Steroid-induced glaucoma ☐ Uveitic glaucoma ☐ Neovascular glaucoma ☐ Traumatic glaucoma ☐ Inflammatory glaucoma ☐ Refractory glaucoma	
Type of eyes:	☐ Phakic ☐ Pseudophakic	
Glaucoma severity or stage:		
Baseline Characteristics		
IOP (mm Hg):		
Number of glaucoma medications:		
Treatment-naive or treatment-experienced (specify):	☐ Treatment-naive ☐ Current/previous pharmacotherapy: _____ ☐ Previous laser therapy: _____ ☐ Previous MIGS: _____ ☐ Previous filtration surgery: _____	
Relevant comorbidities (e.g., cataract):		

POPULATION – Comparator Group		
Number of patients/eyes:	Patients, n = ___	Eyes, n = ___
Age:		
Sex/Gender:		
Race:		
Type of glaucoma:	☐ Primary open-angle glaucoma ☐ Secondary open-angle glaucoma ☐ Angle-closure glaucoma ☐ Pigmentary glaucoma ☐ Pseudoexfoliation glaucoma ☐ Steroid-induced glaucoma ☐ Uveitic glaucoma ☐ Neovascular glaucoma ☐ Traumatic glaucoma ☐ Inflammatory glaucoma ☐ Refractory glaucoma	
Type of eyes:	☐ Phakic ☐ Pseudophakic	
Glaucoma severity or stage:		
Baseline Characteristics		
IOP (mm Hg):		
Number of glaucoma medications:		
Treatment-naive or treatment-experienced (specify):	☐ Treatment-naive ☐ Current/previous pharmacotherapy: _____ ☐ Previous laser therapy: _____ ☐ Previous MIGS: _____ ☐ Previous filtration surgery: _____	
Relevant comorbidities (e.g., cataract):		

IOP = intraocular pressure.

INTERVENTION and COMPARISON	
Intervention:	☐ **Performed alone** ☐ **Performed in conjunction with cataract surgery (i.e., phacoemulsification)** ☐ ECP ☐ Trabectome ☐ Kahook Dual Blade ☐ iStent (first generation) ☐ iStent Inject (second generation) ☐ CyPass Micro-Stent ☐ GATT ☐ XEN 45 Gel Stent ☐ XEN 63 Gel Stent ☐ XEN 140 Gel Stent Number of MIGS devices: _____
Comparator (provide details where applicable):	☐ A different MIGS device or procedure: _____ ☐ Pharmacotherapy alone: _____ ☐ Laser therapy: _____ ☐ Filtration surgery: _____

INTERVENTION and COMPARISON	
	☐ A different MIGS device or procedure in conjunction with cataract surgery (i.e., phacoemulsification): _____ ☐ Filtration surgery performed in combination with cataract surgery (i.e., phacotrabeculectomy) ☐ Cataract surgery (i.e., phacoemulsification) alone

REPORTED OUTCOMES	
Primary (including definition):	
Secondary (including definition):	
Length of follow-up:	
Loss to follow-up:	

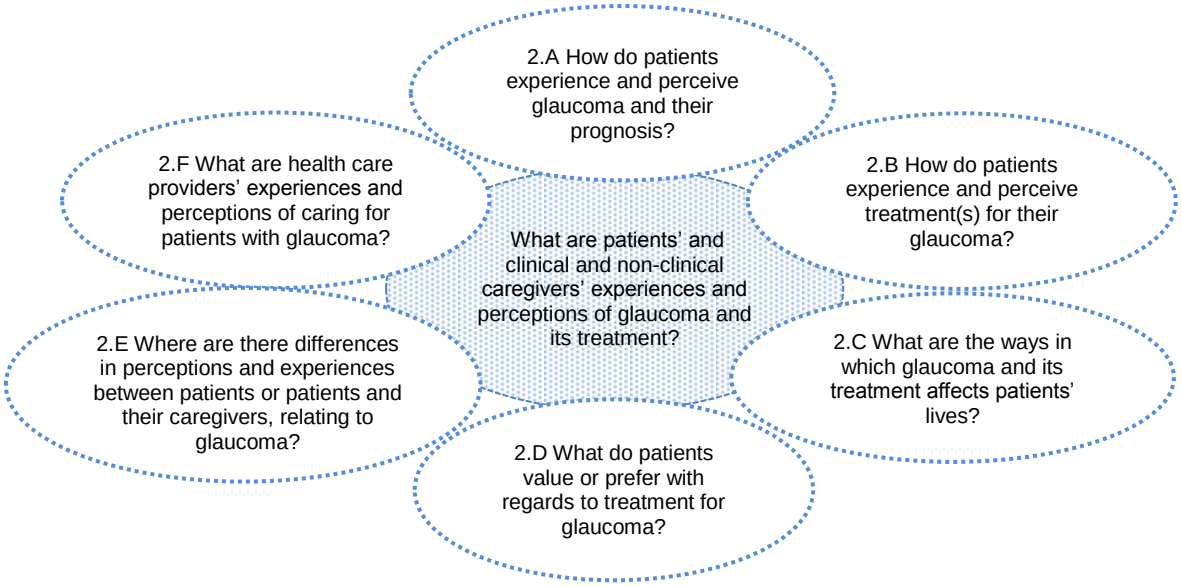
RESULTS[a] (to be completed for each follow-up time point)		
Follow-up Time Point: _____	**Intervention Group**	**Comparison Group**
Sample size at follow-up time point		
IOP		
Absolute IOP (mm Hg): ☐ **Medicated** ☐ **Unmedicated** ☐ **Not specified**		
Change in IOP from baseline (absolute; mm Hg): ☐ **Medicated** ☐ **Unmedicated** ☐ **Not specified**		
% change in IOP from baseline: ☐ **Medicated** ☐ **Unmedicated** ☐ **Not specified**		
% of patients with IOP ≤ _____ [specify threshold]		
Glaucoma Medications		
Number of glaucoma medications (absolute):		
Change in number of glaucoma medications from baseline (absolute):		
% change in number of glaucoma medications from baseline:		
Quality of Life		
Quality of life (absolute):		
Change in quality of life from baseline (absolute):		
% change in quality of life from baseline:		
Visual Field Loss		
Visual field (absolute):		
Change in visual field from baseline (absolute):		

RESULTS[a] (to be completed for each follow-up time point)		
% change in visual field from baseline:		
Visual Impairment		
Measurement of visual impairment:		
Absolute visual impairment:		
% change in visual impairment from baseline:		
Visual Acuity		
Visual acuity (absolute):		
Change in visual acuity from baseline (absolute):		
% change in visual acuity from baseline:		
Adverse Events and Complications[b]		
Intraoperative adverse events: (specify type, n and %)		
Post-operative adverse events: (specify type, n and %)		
Covariates included in model (if applicable)		

[a] All results to be extracted as means ± standard deviation, unless otherwise specified.
[b] Examples include: transient IOP fluctuation, infection, hyphema, hypotony, device occlusion or malposition, need for additional procedure(s), or cataract formation.

Appendix 6: Primary and Secondary Research Questions and Evidence Synthesis — Patients' and Caregivers' and Clinical and Non-clinical Caregivers' Perspectives and Experiences Review

Figure 2: Primary and Secondary Research Questions Guiding Qualitative Evidence Synthesis



Appendix 7: Data Extraction Forms — Patients' and Clinical and Non-clinical Caregivers' Perspectives and Experiences Review

Table 3: Sample Table of Included Studies

First Author, Publication Year, Country, Funding Source	Study Design [a]	Study Objectives	Study Setting	Sample Size	Inclusion Criteria	Data Collection

[a] Analytic strategy where study design or qualitative approach is not reported.

Table 4: Sample Table of Study Characteristics

First Author, Publication Year	Sample Size	Sex (% Male)	Age in Years	Socio-Demographic Characteristics[a]	Time Since Diagnosis	Glaucoma Treatment

[a] Socio-demographic characteristics include ethnicity, measure of income or education, employment.

Appendix 8: Quality Appraisal Extraction Form — Patients' and Caregivers' Perspectives and Experiences Review

Table 5: Table of Quality Appraisal

First Author, Publication Year		Credibility	Dependability	Transferability	Confirmability
	Strengths				
	Limitations				
	Strengths				
	Limitations				
	Strengths				
	Limitations				