Norwegian Institute of Public Health

Protocol

Minimally Invasive Glaucoma Surgery (MIGS) for individuals with open-angle glaucoma. A health technology assessment

Project number:	ID2018_072
Plan prepared:	October 2019

Title
Minimally Invasive Glaucoma Surgery (MIGS) for individuals with open-angle glaucoma. A health technology assessment

Short title
HTA of MIGS for individuals with glaucoma

Short project description
The Ordering Forum, Regional Health Authorities (RHA Forum) commissioned Norwegian Institute of Public Health (NIPH) to carry out a HTA of MIGS, through the National System for Managed Introduction of New Health Technologies. We will assess the relative effect, safety, and cost-effectiveness of the method(s) for treatment of individuals with open-angle glaucoma.

Short summary
Glaucoma refers to a group of diseases in which there is progressive damage to the optic nerve. Globally, glaucoma is considered as the leading cause of irreversible vision loss and one of the leading causes of blindness (1;2). In Norway, approximately 40,000 individuals have diagnosed glaucoma (3). Glaucoma incidence is expected to increase in the coming years because of demographic changes (4). MIGS represents a class of various new surgical procedures and devices developed since the early 2000s in an attempt to provide a minimally invasive surgical approach to glaucoma treatment that limits damage to the conjunctiva. Experts suggest that MIGS may result in shorter procedure times and patient recovery times than traditional surgical procedures, making it possible to perform MIGS treatment at an earlier stage of glaucoma. The indications for each specific MIGS-procedure can vary depending on its mechanism of action and the individual patient's target intraocular pressure (IOP). MIGS procedures and devices can be used as a stand-alone procedure or in conjunction with cataract surgery. In general, there is a growing demand for use of MIGS both in Norway and globally (5;6). This HTA will assess the relative effect, safety, and cost-effectiveness of the method(s) for treatment of individuals with different types of open-angle glaucoma (the most common type of glaucoma). We will report health gain, resource use, severity, and cost effectiveness according to the prioritization criteria (7). In addition, we will aim to include patient partners' perspectives and experiences, organizational consequences, and ethical issues related to MIGS use in Norway.

Norsk

Protokoll

Minimal-invasiv glaukomkirurgi (MIGS) for individer med åpenvinklet glaukom. En metodevurdering

Prosjekt nummer:	ID2018_072
Plan utarbeidet:	Oktober 2019

Tittel
Minimal-invasiv glaukomkirurgi (MIGS) for individer med åpenvinklet glaukom. En metodevurdering

Kort tittel
Metodevurdering av MIGS for individer med glaukom

Kort prosjektbeskrivelse
Bestillerforum regionalt helseforetak (RHF) har gitt Folkehelseinstituttet (FHI) i oppdrag å utarbeide en fullstendig metodevurdering for MIGS, gjennom det nasjonale systemet for introduksjon av nye metoder. Vi vil undersøke relativ effekt, sikkerhet, og kostnadseffektivitet av metoden(e) til behandling av individer med åpenvinklet glaukom.

Kort oppsummering
Glaukom refererer til en sykdomsgruppe som innebærer progressiv ødeleggelse av synsnerven. Globalt betraktes glaukom som den vanligste årsaken til irreversibelt synstap og en av de vanligste årsakene til blindhet (1;2). I Norge er om lag 40 000 individer diagnostisert med glaukom (3). Insidensen er forventet å øke i påfølgende år på grunn av demografiske endringer (4). MIGS representerer en gruppe av nye kirurgiske prosedyrer og utstyr utviklet, siden tidlig 2000-tallet, i forsøk på å levere en minimal-invasiv kirurgisk tilnærming til glaukom behandling, som begrenser skade på øyets bindehinne. I følge eksperter kan MIGS resultere i kortere prosedyretider og restitusjonstid for pasient sammenlignet med tradisjonelle kirurgiske prosedyrer, som gjør det mulig å utføre MIGS på et tidligere sykdomsstadie. Indikasjonene for hver enkelt MIGS-prosedyre kan variere avhengig av dets virkningsmekanisme og pasientens individuelle mål for intraokulært trykk (IOP). MIGS prosedyrer og utstyr kan utføres alene eller i kombinasjon med katarakt kirurgi. Generelt, er det økende etterspørsel for bruk av MIGS i Norge og globalt (5;6). Denne metodevurderingen vil undersøke relativ effekt, sikkerhet, og kostnadseffektivitet av metoden(e) for behandling av individer med ulike typer åpenvinklet glaukom (den vanligste formen for glaukom). Vi vil rapportere helsegevinst, ressursbruk, alvorlighet, og kostnadseffektivitet i henhold til prioriteringskriteriene (7). I tillegg tar vi sikte på å inkludere brukerrepresentanters' perspektiv og erfaringer, organisatoriske konsekvenser, og etiske aspekter relatert til bruk av MIGS i Norge.

Project category and commissioner	
Product:	Health technology assessment
Thematic areas:	Surgery, eye disease, health technology assessment
Commissioner:	Ordering Forum, The Regional Health Authorities (RHA Forum) (Bestillerforum RHF), consisting of four medical directors (one for each regional health authority) and two delegates from the Norwegian Directorate of Health
Project management and participants	
Project leader:	Ulrikke Højslev Lund, Health Economist
Responsible for the project:	Øyvind Melien, Department Director
Internal project participants:	Julia Bidonde, Researcher Beate Charlotte Fagerlund, Health Economist Martin Lerner, Senior Advisor Lien Nguyen, Information Specialist Bjarne Robberstad, Health Economist
External clinical experts:	Jon Henrik Tveit, MD, Oslo University Hospital Marit Fagerli, MD, Trondheim University Hospital Hildegunn Halvorsen, MD, Haukeland University Hospital, Bergen Are Lindland, MD, Hospital of Southern Norway, Arendal
External patient partners:	Asle Haukaas, Board Member, Norwegian Glaucoma Association Mette Mellem, Low Vision Teacher, Norwegian Association of the Blind and Partially Sighted Arne Tømta, Low Vision Teacher, Norwegian Association of the Blind and Partially Sighted
External ethicist:	Lars Øystein Ursin, Associate Professor, Department of Public Health and Nursing, Norwegian University of Science and Technology
Plan for replacement by project participants' absence:	Replacements will be decided by the person responsible for the project
Internal reviewers:	For the protocol: Hege Kornør and Kåre Birger Hagen For the full report: To be decided
External reviewers:	For the protocol: Clinical experts and patient partners participating in this project. For the full report: To be decided

Commission

On June 21st, 2018 Glaukos Corporation submitted a proposal for a new national HTA regarding the use of trabecular bypass MIGS device implantation with iStent inject in patients with primary open-angle glaucoma, pseudoexfoliative glaucoma or pigmentary glaucoma (8). The RHA Forum in the National System for Managed Introduction of New Health Technologies, assessed the proposal, together with a horizon scanning report (9), on September 24th 2018, and commissioned NIPH to conduct a single HTA (i.e. the assessment of a single MIGS device). Because there several suppliers of MIGS devices, a single HTA is not appropriate, and on October 22th 2018 the RHA Forum instead commissioned NIPH to conduct a multiple HTA to assess relative effect, safety, cost-effectiveness of all MIGS devices for treatment of individuals with glaucoma in Norway (10;11).

Goals

According to the prioritization criteria in Norway (7), the goals of this HTA are to

1) Systematically identify, assess and summarize available research evidence regarding clinical effect and safety of (selected) MIGS devices and procedures versus each other or another comparator (i.e. pharmacotherapy, laser therapy, filtration surgery, cataract surgery), both as a stand-alone procedure or performed in combination with cataract surgery, in the treatment of open-angle glaucoma.
2) Conduct a health economic evaluation and quantify the severity criterion by calculating absolute shortfall for individuals with glaucoma that receive conventional care. We will report health gain, resource use, severity, and cost effectiveness of MIGS compared to conventional care in a Norwegian setting.
3) Assess organisational challenges and consequences linked to establishing MIGS as a treatment option in Norway.
4) Assess potential ethical issues raised by the use of MIGS in treatment of glaucoma in Norway.

We will include patient partners' in the assessment team in order to understand their own perspectives and experiences regarding glaucoma treatment and healthcare services, as well as the perspectives of their caregivers.

Background

Glaucoma

Glaucoma refers to a group of disease, in which there is a progressive damage to the optic nerve, which can lead to visual loss (1). Optic nerve damage can occur in the event of an imbalance between access and drainage of eye fluid in the area between iris and cornea, where drainage are prevented and the eye pressure increases (figure 1) (12). Glaucoma is a slowly progressing disease, sometimes called the "silent thief of sight". Because central vision often remains intact as the disease progresses, irreversible harm can result before the patient notices "tunnel visions" or other types of visual impairment. Early diagnosis and appropriate treatment could help prevent permanent visual defects and blindness. The cause of glaucoma remains unknown. However, some factors have been identified to possibly increase the risk of developing the

disease. Examples of such risk factors are: age, family history, ethnicity, eye injuries, long-term cortisone treatment, high IOP, diabetes and cardiovascular disease (13-15). There are several types of glaucoma, the two main types being primary open-angle glaucoma (POAG) and closed angle glaucoma, which are marked by an increase of intraocular pressure (IOP), or pressure inside the eye (16).

Globally, glaucoma is regarded as the leading cause of irreversible vision loss and one of the leading causes of blindness (1;2). According to Peters et al., there is a 26.5% risk of blindness in one eye after 10 years and a 5.5% for bilateral blindness. After 20 years the risks are 38.1% and 13.5% respectively (17).

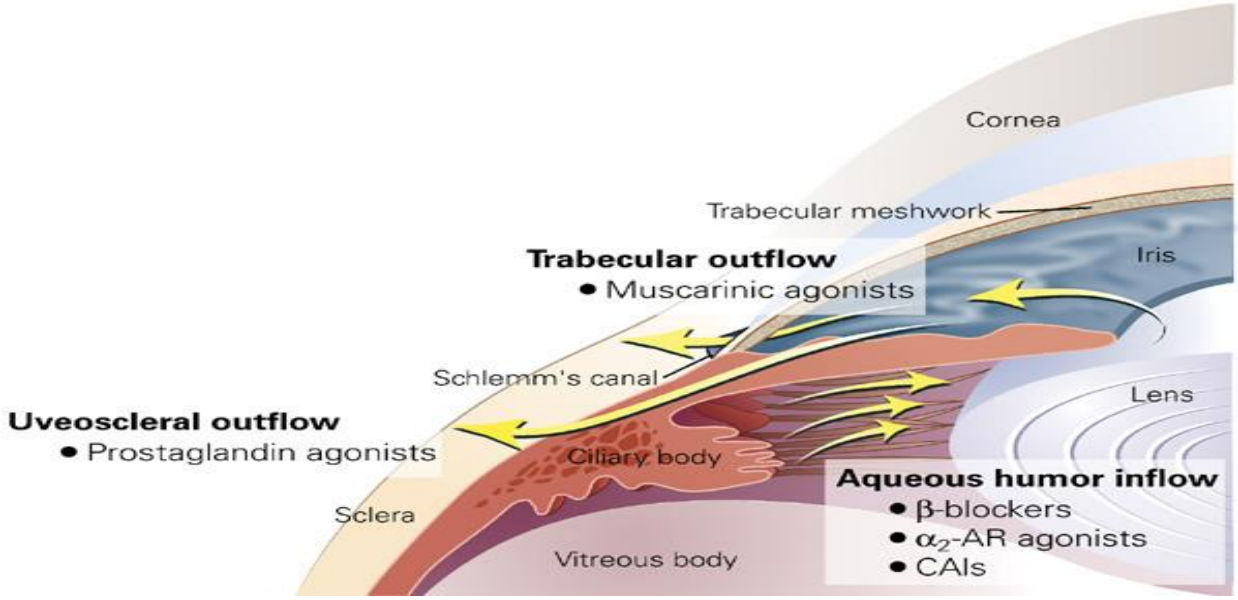

Figure 1. Illustration of the drainage route for aqueous humor flow (18).

Incidence and prevalence

In Norway, approximately 40,000 individuals have diagnosed glaucoma. Glaucoma is most common among the elderly population. It is estimated that 2.19% of the population aged 40 and over have glaucoma; the estimated prevalence of the whole population is 0.92% (3). Glaucoma incidence is expected to increase in the coming years because of demographic changes that result in an ageing population and an increase in life expectancy (4).

Current glaucoma treatment in Norway

There is no curative treatment for glaucoma and vision loss from glaucoma is irreversible. The goal of current treatment is to address the only reversible risk factor for glaucoma, IOP, and thereby to prevent further nerve damage and loss of vision. By achieving a significant and sustained decrease in IOP the subsequent risk of disease progression is reduced and the quality of life is preserved (1). Choice of treatment is often dependent on the severity of the disease (19).

The conventional treatment for glaucoma upon diagnosis of the disease is to introduce topical medication with an IOP-lowering eye drop as monotherapy or a combination of eye drops with

different mechanisms of action (pharmacotherapy). If pharmacotherapy does not adequately control the IOP, laser treatment is usually the next step. This treatment, known as laser trabeculoplasty, directs a laser beam at the trabecular meshwork, the drainage system of the eye. Generally, this is a short procedure performed in outpatient clinics. However, laser therapy is not recommended for some individuals with glaucoma because of contraindications. With more severe cases of glaucoma, and when pharmacotherapy and laser treatment has failed to result in adequate IOP, a final step is to offer glaucoma surgery. The most common glaucoma surgery is trabeculectomy followed by tube implantation, both provide an alternate drainage for the eye fluid, thus lowering IOP. Both of these techniques have been shown to be effective, but are more complex interventions with a considerable risk of serious complications, longer recovery time and potentially lifelong discomfort to the patient. The success rate for these surgical procedures decreases with repeated surgery. Continued pharmacotherapy is usually required after both laser therapy and surgery, and even when surgery is performed with use of "off labeled antimetabolites" (internationally widely used and accepted). Another option is destruction of the ciliary body, the structure in the eye where eye fluid is produced, through laser cyclophotocoagulation (CPC) (5;20;21).

Minimally Invasive Glaucoma Surgery

MIGS (Minimally Invasive Glaucoma Surgery) is a potential surgical alternative to current treatment of glaucoma. Rather than reflecting a single surgical procedure or device, MIGS represents a class of various new surgical procedures and devices developed since the early 2000s in an attempt to provide a minimally invasive surgical approach to glaucoma treatment that limits damage to the conjunctiva (5;6). Experts suggest that, in addition to causing minimal or no damage to the conjunctiva, MIGS may also result in shorter procedure times and patient recovery times than traditional surgical procedures, making it possible to perform MIGS treatment at an earlier stage of glaucoma. The success of future surgery may be improved when there is minimal or no damage to the conjunctiva. According to experts, the combination of positive effects could make MIGS a good option as the first surgical treatment, following laser trabeculoplasty. It might also be possible to use MIGS as a first line treatment for selected patients who need only modest IOP lowering (5).

As of October 2019, NIPH was aware of 15 MIGS devices and procedures. The indications for each specific MIGS-procedure can vary depending on its mechanism of action and the individual patient's target IOP. MIGS can be used as a stand-alone procedure or in conjunction with cataract surgery, possibly with a higher success rate than traditional glaucoma surgery in combination with cataract surgery (5). MIGS can be categorized by recipient reservoir, as Schlemm's canal/Trabecular meshwork (TM), suprachoroidal space or subconjunctival space, according to where fluid is redirected during the procedure (figure 2) (6). Recently, there has been a growing demand for use of MIGS both in Norway and globally. To the best of our knowledge, several hospitals in Norway currently offer some type of MIGS to individuals with glaucoma (5).

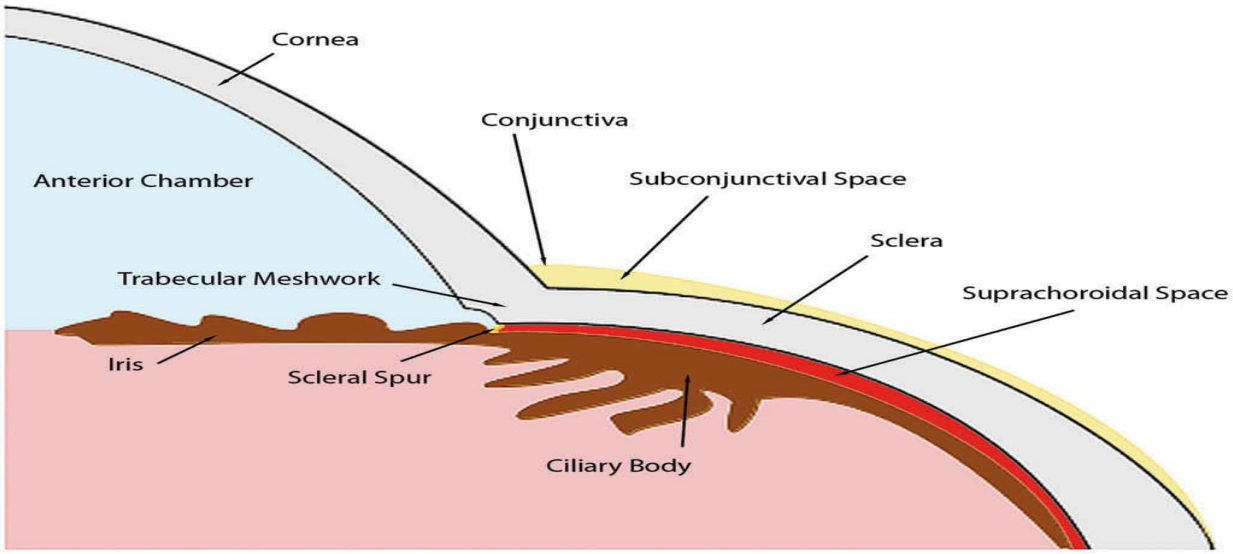

Figure 2. Illustration of spaces targeted by injectable and implantable devices (22).

Summary of CADTH's report: Efficacy

NIPH have identified a MIGS HTA published in January 2019 by the Canadian Agency for Drugs and Health Technology (CADTH). The conclusion from the CADTH report on optimal use of MIGS is that there is insufficient evidence on clinical effectiveness and safety of MIGS versus comparators and there is no definitive evidence on which specific MIGS might be preferable. Although pointing at limitations in the evidence base, MIGS is suggested to have a potential role in the treatment of adult patients with glaucoma if some factors are considered and disclosed to patients. Factors which include, among others, the diversity of MIGS options, surgeon's experience and health care system related issues such as geographical location and financial considerations (15).

Methods

This HTA will re-use and adapt sections of a MIGS HTA published in January 2019 by the Canadian Agency for Drugs and Health Technology (CADTH) (15). The NIPH technical team contacted CADTH and the two agencies agreed on collaborating in this process. We will indicate in the sections below when the information comes from CADTH's HTA report by citing it appropriately.

The NIPH technical team wrote this protocol, which once finalised, will be published on the NIPH website. Any deviations from the protocol will be disclosed in the final report.

Studies

Eligibility criteria

Our framework for searching for and selecting relevant literature for our HTA is outlined in the population, intervention, comparator and outcomes (PICO) table 1 below. We adapted the PICO

from CADTH (15) as follows: population and interventions, we focus on open angle glaucoma only and MIGS were based on Norwegian clinical expert opinion; outcomes were selected by the NIPH technical team, clinical experts and patient partners.

Table 1. Inclusion and exclusion criteria (adapted from CADTH (15))

PICO	Inclusion	Exclusion
Population	• Adults (i.e., age of ≥ 18 years) with open-angle glaucoma (primary and secondary, e.g. pigmentary, pseudoexfoliative)	• Adults with juvenile-onset/congenital glaucoma • Adults with closed-angle glaucoma • Adults with ocular hypertension but no evidence of optic nerve damage or formal diagnosis of glaucoma • Animal or ex vivo populations
Intervention	Any of the following MIGS, categorized by recipient reservoir, as stand-alone procedure or in conjunction with cataract surgery: **Schlemm's canal / Trabecular meshwork (TM)** ***Increasing trabecular outflow by bypassing the TM using a device*** • iStent • iStent inject • Hydrus ***Increasing trabecular outflow by bypassing the TM using tissue ablation/removal*** • Trabectome • Kahook Dual Blade ***Increasing trabecular outflow by bypassing the TM via 360º suture*** • GATT (Gonioscopy Assisted Transluminal Trabeculotomy) • iTrack • Visco360 • Trab360 **Suprachoroidal space** • Solx Gold Shunt • iStent Supra • Aquashunt **Subconjunctival space** • Xen Gel Stent (45 / 63 / 140) • InnFocus Microshunt **Aqueous humor reduction** • Endoscopic cyclophotocoagulation (ECP)	
Comparator	• A different MIGS device or procedure by itself or performed in conjunction with cataract surgery	

	• Pharmacotherapy alone • Laser therapy (e.g., excimer laser trabeculotomy or selective laser trabeculoplasty) • Filtration surgery – trabeculectomy, including non-penetrating surgery (e.g. viscocanalostomy, deep sclerectomy) • Filtration surgery – aqueous shunt implantation (e.g. Ahmed glaucoma valve, Baerveldt glaucoma implant) • Filtration surgery performed in combination with cataract surgery (i.e., phacotrabeculectomy) • Cataract surgery (i.e., phacoemulsification) alone
Outcome	**Clinical Effectiveness** ***Primary outcome:*** • IOP* • IOP fluctuation* ***Secondary outcomes:*** • Quality of Life (QoL) • Number of glaucoma medication use* • Vision related QoL* • Visual field loss* • Visual impairment • Visual acuity • Retinal Nerve Fibre Layer (RNFL) thickness* **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, suprachoroidal haemorrhage, visual loss, endothelial cell loss) • Adverse effects of pharmacotherapy (e.g. tinging or redness of eyes, blurred vision, headache, bradycardia or bronchospasm, change of iris color (in individuals with light-colored eyes taking prostaglandin analogues))

IOP: intraocular pressure; MIGS: minimally invasive glaucoma surgery. *These outcomes were identified as being of particular importance to patients in the input received from patient partners.

Language

The search has no language limitations; the NIPH technical team is able to translate literature in Spanish, Swedish, English, French, German, and Norwegian. We will translate any studies that meet our PICO.

Study design (Adapted from CADTH)

We conducted a preliminary scoping review to identify other evidence synthesis available (i.e. existing HTAs) for the past 5 years. We found an HTA done in the Malaysia (23) and CADTH's report published in January 2019 (15).

We will adapt and update CADTH's search for primary studies to address clinical effectiveness and safety of MIGS for adults with open-angle glaucoma. We will open the search to other languages in order to capture literature applicable or from Scandinavian countries. The search strategy will be re-run from 2000 to present, and duplicate studies based on CADTH's findings removed, in order to screen new records meeting our PICO criteria (15).

First, we will include systematic reviews meeting our PICO published in the last 5 years.

Comparative study designs:
- Randomized controlled trials (RCTs)
- Non-randomized controlled clinical trials such as cohort studies or 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
- Studies with triple surgery (MIGS + 2 other non-MIGS interventions)

Literature search

Using CADTH's search strategy as a base for the creation of this assessment search, and given there are differences in the PICO criteria, a research librarian will perform a new literature search. She will use a peer-reviewed search strategy. The relevant electronic databases to be searched are as follows: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily [1946-], OVID EMBASE [1974-], Cochrane Database of Systematic Review (Wileys & Sons), Cochrane Central Register of Controlled Trials (Wileys & Sons), DARE (Centre for Reviews and Dissemination) and CINAHL (EBSCO).

We will search Clinicaltrials.gov (U.S. National Library of Medicine) and International Clinical Trials Registry Platform (World Health Organization) for ongoing, completed and terminated clinical trials.

In addition, we will search various manufacturers' web pages for relevant publications regarding MIGS-treatment. We will also search in relevant websites from selected sections in the CADTH grey literature checklist (*Grey Matters: a practical tool for searching health-related grey literature*), HTAi Vortal and the New York Academy of Medicine. Finally, we will perform reference searches, where we specifically search for relevant studies as referenced in included studies, as well as in systematic reviews.

Regular alerts will be established to update the searches until the publication of the final report on databases that provide alert services. Alerts will be reviewed at two stages: first before the data extraction and analysis at which time studies meeting the selection criteria will be incorporated into the analysis of the final report. Then, any studies that are identified after this

period will be described in the discussion and recorded in an appendix for future versions of this report.

Search strategy

The main search concepts will include terms such as glaucoma, minimally invasive glaucoma surgery and minimally invasive glaucoma devices.

Filters

The search will be limited to year 2000 to present.

Selection of studies

We will select studies found in the literature search in a two-step selection strategy:

1) Title and Abstract Screening: two researchers will independently screen titles and abstracts using Covidence software (24), selecting only those that answer out research question.
2) Full-text Screening: two researchers will independently screen the full-text articles for inclusion in the HTA.

We will conduce both steps following the eligibility criteria listed above (i.e. PICO). Disagreements in either of the two steps will be resolved through a consensus meeting, and a third researcher will be involved when needed it.

We will report the selection process in a PRISMA flowchart. We will provide a list of excluded studies, with reasons, after full text review in an Appendix.

Assessment of methodological quality: Individual studies

In the event NIPH includes articles included in the CADTH's report, the team will access the assessment from CADTH and check it in 1-2 studies for accuracy. If satisfactory, we will use CADTH's assessment for those studies included in both HTAs.

In the event we found new (i.e. published after CADTH cut-off date) or different (i.e. in other languages), studies we will proceed as follows:

Two independent researchers will assess the quality of the included primary studies using an appropriate risk-of-bias-tool. We will use AMSTAR II for systematic reviews (25) follow the methods described in Cochrane Risk of Bias assessment toll for randomized control trials (26) and the Risk of Bias in non-RCTs (a modified/simplified version) of the ROBINS-I tool (27).

Any disagreements will be resolved through consensus between the researchers, or by consultation with a third party if needed.

The results of the risk of bias will be presented narratively and accompanied by tables showing researchers judgements. This will aid in understanding strength and limitations of 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 for Recommendations Assessment, Development, and Evaluation (GRADE) framework (28), Quality assessment will be performed by one reviewer and verified by a second reviewer, and will be presented in GRADE evidence profile tables (29) . These assessments will be used to provide explicit judgements about the certainty in the evidence.

The certainty of evidence is classified as follows in table 2:

Table 2. GRADE classification

Quality level	Definition	Symbols
High	We are very confident that the true effect lies close to that of the estimate of the effect	⨁⨁⨁⨁
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	⨁⨁⨁◯
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	⨁⨁◯◯
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	⨁◯◯◯

Processing data

Data extraction

If NIPH includes articles included in the CADTH's report, the team will contact to CADTH to obtain extracted data (as per Table 3). If, in addition, we find new (i.e. published after CADTH cut-off date) or different (i.e. in other languages), studies we will proceed as follows:

Data will be extracted into electronic files created and piloted for this project to facilitate independent data extraction. One researcher will extract data and a second one will check for accuracy. Any potential disagreements will be resolved through consensus, or by consultation with a third researcher. If necessary (e.g. if data are unintelligible), we will contact the authors for them to provide us with sufficient information to use in our HTA.

Information we will extract includes (table 3):

Table 3. Data extraction information

	Information to be extracted
The study	First authors's name, publication year, publication title, country where the study was conducted, trial registration number, eligibility criteria, follow-up time, funding source
Methods	Study design and objectives, inclusion and exclusion criteria, number of study centres and locations, study setting, primary and secondary outcomes, analyses of interest
Population	Numbers of participants in each group or eyes, age, gender, type of glaucoma, glaucoma severity/stage, presence of cataracts or other comorbidities of interest, disease duration
Comparator	Any comparator used
Results and conclusions	Information regarding the outcomes and subgroups of interest, means and standard deviations for test baseline and post-intervention, and follow up
Note	Funding for trial and notable declarations of interest of trial authors

Analyses

We will present the study characteristics and findings using a narrative synthesis and within summary tables. If more than one study is included, we may pool the studies using random effects meta-analyses; pooling studies requires that the data are sufficiently homogeneous in clinical, methodological and statistical aspects. We will conduct separate analyses for randomized and non-randomized studies.

We will analyze dichotomous data as relative risk and 95% confidence intervals (CIs). Continuous data will be pooled when possible using mean differences (MD) and corresponding 95% CIs. We will preferentially use adjusted effects measures if reported. We will use RevMan software to generate forest plots for individual summary estimates (30).

We will assume a minimal clinically important difference (MCID) of 1 mmHg as being clinically relevant, dependent on condition. In the absence of literature in this area, we based this MCID on expert opinion (5).

Unit of Analysis: We will record, for each eligible study, whether randomization was at the level of the participant or the eye.

Dealing with missing data: When numerical data are missing, we will contact the authors of studies and request additional data required for analysis. We will contact authors using open-ended questions to obtain the information needed to assess risk of bias or the treatment effect, or both. When numerical data are available only in graphic form, we will use Engauge version 5.1 to extrapolate means and standard deviations by digitalizing data points on the graphs.

Assessment of Heterogeneity: We will assess statistical heterogeneity using graphical presentations (e.g. forest plots) and calculations of Cochran's chi square test and the I^2 statistics, which quantifies the variability in the effect estimates due to heterogeneity rather

than chance. We will interpret heterogeneity according to the guidance in the Cochrane handbook as follows: 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. We will interpret a P value from the Chi^2 test that is less than or equal to 0.10 as evidence of statistical heterogeneity.

Assessment of Publication (reporting) Bias: If we identify a large enough sample of studies (10 or more included studies of a given study design and a particular outcome), we plan to produce funnel plots to investigate publication bias. We will visually assess funnel plots and objectively use Egger's regression test and Begg's rank correlation test.

Assessment of outcome reporting bias: For studies published after July 2005 we will screen the Clinical Trials Registry Platform of the World Health Organization (apps.who.int/trials search) for the a priori trial protocol. We will evaluate whether selective reporting of outcomes is present (outcome reporting bias). We will compare the fixed-effect estimate against the random effects model to assess the possible presence of small sample bias in the published literature (i.e. in which the intervention effect is more beneficial in smaller studies). In the presence of small sample bias, the random-effects estimate of the intervention is more beneficial than the fixed-effect estimate.

Subgroup or meta-Regression Analyses (these sections follows CADTH's subgroup analysis categories and is complemented with Norwegian clinical experts input)

If we find a sufficient number of studies, we will examine the following subgroups of interest in exploratory analyses:

- Treatment-naive versus treatment-experienced (e.g., previous laser therapy, previous MIGS, previous filtration surgery), or current/previous pharmacotherapy.
- Primary versus secondary (pseudoexfoliative, pigmentary, uveitic, traumatic, neovascular, other) glaucoma.
- Number of MIGS devices (e.g., one, two, or three iStents, other combinations of several MIGS: iStent in combination with ECP).
- Severity or stage of glaucoma (e.g., early, moderate, or advanced).
- Phakic versus pseudophakic eyes.

Sensitivity Analysis

- Impact of risk of bias.
- Impact of included population composition – in subgroups.
- Tonometry method (applanation/Goldmann, rebound, air-puff, pneumatonometry, other).

Health economic evaluation

In order to assess the cost-effectiveness of MIGS, we will estimate and describe costs and effectiveness related to MIGS and comparator(s) in a Norwegian context. Costs and resource use will be based on information from Norwegian cost databases, Norwegian literature, and Norwegian clinical experts' opinions. Efficacy estimates will be taken from the results of the

systematic literature review, and we will make final decisions about the appropriate methods for the health economic evaluation when the efficacy results are available. If there exist sufficient documentation on efficacy we will perform a cost-per-quality-adjusted-life-year (QALY)-analysis (Cost-utility analysis: CUA), and develop a probabilistic Markov decision analytic model. If we do not find sufficient documentation, other analyses can be more appropriate. In addition, we will undertake a five-year budget impact analysis of a potential introduction in Norway of MIGS as a treatment option for individuals with glaucoma. We will use the health care perspective in this evaluation, which is relevant for prioritization of interventions within a fixed health care budget if the aim of the decision maker is to maximize health.

Structure, assumptions and input in a potential health economic model will be based on feedback from clinical experts, patient partners, Norwegian registers and literature. In addition, we will perform a literature search to identify previous health economic evaluations of MIGS for individuals with glaucoma compared to conventional treatment. We will summarize results from any relevant identified studies. As cost-effectiveness results from economic models developed in other countries do not reflect a Norwegian context, they cannot inform a decision about introducing a treatment in Norway. We will consider, however, the following options: 1. requesting permission to use an existing model with Norwegian costs, resource use and epidemiologic data as inputs, 2. basing our own health economic model on the structure of a relevant model in an existing study, for example, the CADTH model, and reusing relevant parameters where possible (15).

Organizational consequences

We will assess organizational challenges and consequences linked to a potential establishment of MIGS as a treatment option in Norway. The assessment will be based on feedback from clinical experts related to current organization and capacity.

Ethics

We will assess potential ethical social and cultural challenges regarding the use of MIGS for treating glaucoma. The purpose is to identify and reflect on key ethical concerns that should be considered when comparing the relative benefits and harms of MIGS versus other treatments of glaucoma in adults and in Norway. The methodology of the ethics assessment will be to go through the following steps: 1. Describe the situation with emphasis on the ethically relevant aspects and challenges. 2. Identify the involved stakeholders and describe their views and interests. 3. Analyse the ethical challenges and possible consequences in terms of the four principles (autonomy, beneficence, non-maleficence, and justice) and relevant guidelines and legal framework. 4. Discuss alternative actions and solutions. These steps are chosen to fit the central ethical issues raised by using MIGS devices and procedures, based on the methodologies used or discussed in relevant HTA ethics guidelines and reports (31-33).

Patient Perspective and Experiences

We will incorporate patient input and experiences in this HTA through patient consultations at early stages (i.e. scoping phase). We will reach out to Norwegian patient organizations representing those with visual impairments and those with glaucoma. We will invite the patient partners who are interested in participating to join the technical team and clinical experts in the initial group meeting. Their participation will help the technical team understand which important outcomes must be included in the assessment, current experiences with Norwegian healthcare services and if possible, they will help us understand what the minimally important clinical differences are.

The Norwegian Institute of Public Health peer review process

Two external clinical experts, one external health economist and two internal research directors will be invited to review the report and provide feedback. Subsequently, it will be approved by an internal group at NIPH before submission to the commissioner.

Time schedule, tasks and publication

Time schedule

The project started after formation of the technical team including NIPH staff, all clinical experts and patient partners in May 2019, and is expected to finish May 2020.

Tasks

The tasks planned in the project are described in table 4 below.

Table 4. Tasks planned in the project

Task	Responsible	Start	Days	End
Find all internal project participants (team) at NIPH	ØM	-	-	27.03.2019
Find external clinical experts and patient partners	RHA Forum (Bestillerforum RHF) /ØM	-	-	02.05.2019
Start-up meeting with external clinical experts and patient partners	UHL	14.06.2019	-	14.06.2019
Write draft protocol and internal project group review	UHL	06.05.2019	43	18.06.2019
External review of protocol (clinical experts and patient partners)	UHL	18.06.2019	104	30.09.2019
Internal peer-review of protocol	UHL	18.06.2019	8	26.06.2019
Find external ethicist	ØM/UHL	13.08.2019	36	18.09.2019
Revise and finalize protocol	UHL	19.08.2019	50	08.10.2019
Submittal and approval of protocol	Head of departments/UHL	08.10.2019	-	-
Literature search	LN	15.07.2019	37	21.08.2019
Select studies according to inclusion and exclusion criteria	ML/JB	21.08.2019	71	31.10.2019

Extract data on efficacy and safety and conduct statistical analyses	ML/JB	01.11.2019	29	30.11.2019
Evaluate the methodological quality in included articles (Risk of Bias)	ML/JB	02.12.2019	15	17.12.2019
GRADE evaluation for outcomes	ML/JB	18.12.2019	2	20.12.2019
Gather data and plan models for health economic analysis	UHL/BCF	19.08.2019	73	31.10.2019
Gather data regarding organizational consequences	UHL/BCF	12.08.2019	80	31.10.2019
Health economic analyses performed	UHL/BCF	01.11.2019	49	20.12.2019
Chapter about ethical issues are written	LØU	07.10.2019	74	20.12.2019
Write first draft HTA report	UHL	06.01.2019	30	05.02.2019
Internal project participants review of first draft report	UHL	05.02.2019	16	21.02.2020
Revise and send draft of report to external clinical experts and patient partners for review	UHL	21.02.2020	21	13.03.2020
Corrections for final draft	UHL	13.03.2020	14	27.03.2020
Internal and external peer-review of report	UHL	30.03.2020	21	20.04.2020
Finalize report	UHL	20.04.2020	21	11.05.2020
Approval and submittal of report	Head of departments/UHL	11.05.2020	14	25.05.2020
Send finalized report to RHA Forum (Bestillerforum RHF) and publish at NIPHs webpage	ØM/UHL	25.05.2020	4	29.05.2020

UHL= Ulrikke Højslev Lund; JB= Julia Bidonde; BCF= Beate Charlotte Fagerlund; ML= Martin Lerner, LN= Lien Nguyen, ØM= Øyvind Melien; LØU= Lars Øystein Ursin.

Publication and Reporting

The report will be prepared considering relevant reporting guidelines (i.e. PRISMA, MOOSE reporting checklist) and will meet the criteria outlined in Measurement Tool to Assess Systematic Reviews (AMSTAR II) checklist (25) .

We will publish the HTA report in English on the homepages of NIPH and the RHA-forum (www.nyemetoder.no), 10 days after submission to the commissioner. It may also be published as a scientific article to reach international readers. Abstracts may be submitted to relevant conferences.

Indexing for the homepage

MIGS, Minimally-Invasive Glaucoma Surgery, Glaucoma, Surgery, Eye Disease, Health Technology Assessment

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