Cochrane Library

Cochrane Database of Systematic Reviews

Adverse events associated with minimally invasive glaucoma surgeries (MIGS) including bleb-forming microstent surgeries (Protocol)

Henein C, Fang CEH, Virgili G, Khaw PT, Azuara-Blanco A

Henein C, Fang CE, Virgili G, Khaw PT, Azuara-Blanco A.
Adverse events associated with minimally invasive glaucoma surgeries (MIGS) including bleb-forming microstent surgeries (Protocol).
Cochrane Database of Systematic Reviews 2022, Issue 12. Art. No.: CD015294.
DOI: 10.1002/14651858.CD015294.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Adverse events associated with minimally invasive glaucoma surgeries (MIGS) including bleb-forming microstent surgeries

Christin Henein[1], Clarissa Ern Hui Fang[2], Gianni Virgili[3], Peng T Khaw[1], Augusto Azuara-Blanco[3]

[1]National Institute for Health Research Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, UK. [2]Manchester Royal Eye Hospital, Manchester, UK. [3]Centre for Public Health, Queen's University Belfast, Belfast, UK

Contact: Christin Henein, c.henein@ucl.ac.uk.

Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New, published in Issue 12, 2022.

Citation: Henein C, Fang CE, Virgili G, Khaw PT, Azuara-Blanco A. Adverse events associated with minimally invasive glaucoma surgeries (MIGS) including bleb-forming microstent surgeries (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 12. Art. No.: CD015294. DOI: 10.1002/14651858.CD015294.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To obtain a comprehensive review of harms following MIGS reported in randomised and non-randomised studies, clinical study reports submitted to regulatory organisations for approval or postmarketing surveillance and registries. We will also examine the design characteristics, risk of bias, and reporting adequacy of pivotal MIGS trials submitted to the US and EU regulatory organisations regarding harms reporting and analyses.

BACKGROUND

Description of the condition

Glaucomas are a group of multifactorial diseases characterised by optic nerve damage associated with visual field loss, which can negatively affect quality of life. The exact cause of glaucoma is unknown; however, research has shown that raised intraocular pressure (IOP) plays some role in its pathogenesis, either directly or indirectly (Weinreb 2014). There is evidence that lowering IOP can help to stop or reduce disease progression (AGIS7 2000; Garway-Heath 2015; Heijl 2002; Kass 2002). Medical, laser and surgical treatments aim to reduce IOP by targeting aqueous production, outflow, or both.

Description of the intervention

Trabeculectomy, a type of glaucoma filtration surgery (GFS), remains the standard procedure and the most commonly performed glaucoma surgery (Murphy 2015). Aqueous shunts have traditionally been used in cases of refractory glaucoma following unsuccessful trabeculectomy, or in people at high risk of GFS failure. Since the early 2010s there has been a marked increase in new glaucoma surgery devices. More recently, with changing trends in glaucoma procedures, surgeons are increasingly opting for minimally invasive glaucoma surgeries (Fujita 2022; Luebke 2021; Yang 2021).

The US Food and Drug Administration (FDA) defines minimally invasive glaucoma surgery (MIGS) devices as "A type of IOP lowering device used to lower IOP using an outflow mechanism with either an *ab interno* or *ab externo* approach, associated with little or no scleral dissection and minimal or no conjunctival manipulation" (FDA 2015). MIGS procedures form a heterogeneous group: they may bypass trabecular meshwork resistance to aqueous flow with microstents into Schlemm's canal, via drainage into the suprachoroidal space, by creating subconjunctival aqueous drainage, or by excision of trabecular meshwork. Cyclodiode procedures use directly observed ablation of ciliary processes under endoscopic control or use of ab externo approaches to reduce aqueous production; other procedures dissect existing outflow channels. Some of these procedures can be performed alone or in conjunction with phacoemulsification.

Regulatory landscape

The USA dominates the implant industry worldwide and provides the largest sales market. Some devices are approved in Europe prior to filing in the USA and long before FDA approval. Class III devices, which are implantable, require a rigorous premarket approval (PMA) review process, whereas most Class I devices and some Class II devices are exempt from PMA review and most FDA good manufacturing practices regulations (FDA 2015; FDA 2018). Manufacturers of exempt devices need only notify the FDA that they are selling the products, and do not require FDA review or clearance. Class II devices considered to pose intermediate risk are reviewed through the 510(k) premarket notification process. According to the FDA, aqueous shunts indicated for refractory glaucoma are Class II devices to be filed through the 510K pathway. The XEN Gel implant was approved in this way and was deemed to be substantially equivalent to predicate devices Ahmed Glaucoma Valve and the EX-PRESS Glaucoma Filtration Device for the management of refractory glaucoma. Minimally invasive devices indicated for use in primary open angle glaucoma (POAG) are categorised as Class III and must be filed through the PMA pathway.

Clinical study reports are often sent to national or regional device regulators such as the FDA and the European Medicines Agency (EMA), which require more harms detail than biomedical journals. ANSI Z80.27 guidance for implantable glaucoma devices recommends sample size calculation based on the primary safety outcome. All adverse events (AEs) should be reported, regardless of whether they are related to the intervention. The FDA in particular (and the EMA to a lesser extent) makes many of its scientific reviews available on its website. The Medical Device Reporting (MDR) regulation contains mandatory requirements for manufacturers, importers, and device user facilities to report certain device-related AEs and product problems to the FDA (FDA 2022). Manufacturers are required to report to the FDA when they learn that any of their devices may have caused or contributed to a death or serious injury.

How the intervention might work

Compared to established procedures for lowering IOP by increasing aqueous outflow or decreasing aqueous inflow, such as GFS and glaucoma surgeries that use aqueous shunts, MIGS is less invasive, so theoretically entails less surgical risk and shorter visual recovery time. With the emergence of new MIGS devices and techniques, robust randomised controlled trial (RCT) evidence is needed to guide their use.

Why it is important to do this review

Medical clinical trials usually include suboptimal reporting of harms outcomes (Pitrou 2009). This is the case in glaucoma surgery trials (Sii 2018), although World Glaucoma Association (WGA) guidelines on design and reporting of such trials are available (Jampel 2009). Researchers have also identified reporting issues in relation to MIGS studies (Mathew 2019).

There is inconsistent reporting of unexpected AEs and scant information on withdrawals or loss to follow-up because of AEs. Data from the early 2020s indicates under-reporting of AEs related to ophthalmic devices through Yellow Card schemes, although manufacturers are required to report these events. The MHRA received fewer than five reports related to glaucoma drainage devices between 2013 and 2017 (McLean 2019).

This modified approach to a Cochrane Review aims to provide patients, clinicians and policy-makers with the most transparent and independent information possible about harms outcomes of MIGS. In addition, it should contribute to improving the European regulatory and postmarket surveillance legal framework. Independent scrutiny of all the evidence relating to harms and complications is necessary to form a complete and unbiased view of their risks and benefits. This review will supplement Cochrane Reviews published by the MIGS consortium (Hu 2022; King 2018; Le 2019; Otarola 2020; Sandhu 2021; Tóth 2019).

OBJECTIVES

To obtain a comprehensive review of harms following MIGS reported in randomised and non-randomised studies, clinical study reports submitted to regulatory organisations for approval or postmarketing surveillance and registries. We will also examine the design characteristics, risk of bias, and reporting adequacy

of pivotal MIGS trials submitted to the US and EU regulatory organisations regarding harms reporting and analyses.

METHODS

Criteria for considering studies for this review

Types of studies

We will use a modified approach to the routine Cochrane process, as described in Jefferson 2014.

Rather than restricting the analysis to RCTs, we will evaluate harms reported in a broad range of studies to build a complete picture of any potential harm and improve generalisability without loss of validity. Eligible studies will have at least one month of follow-up. We will include:

- RCTs;
- non-randomised studies for intervention (NRSI); and
- large case series with a minimum of 100 participants.

Data sources will include:

- clinical study reports to regulatory organisations;
- patient registries;
- large clinical databases; and
- postmarketing surveillance studies.

This review will assess the primary harm data submitted to regulatory organisations by devise manufacturers against harm data published in the literature (from manufacturers and non-manufacturer sources).

We will exclude cluster and cross-over RCTs.

Types of participants

Participants with open angle glaucoma (OAG) of any type, including ocular hypertension, POAG, and normal tension glaucoma. We will exclude glaucoma suspects and participants with angle-closure glaucoma. We will include studies of people with different types of glaucomas if more than 50% of participants have OAG. We will list all treatment arms in the 'Characteristics of included studies' table, even if they are not used in the review. Studies investigating only secondary glaucomas will not be eligible for inclusion. There will be no restrictions on study geographic location, setting, or demographic factors of included participants.

Types of interventions

- Subconjunctival devices
  - XEN Gel implant (Allergan, Ireland); ab interno or ab externo approaches
  - PreserFlo MicroShunt (previously known as InnFocus MicroShunt, Santen, Japan); ab externo approach
- Schlemm's canal devices
  - iStent (Glaukos, Laguna Hills, CA, USA)
  - iStent inject (Glaukos, Laguna Hills, CA, USA)
  - Hydrus Microstent (Ivantis, Irvine, CA, USA)
  - Gonioscopy-assisted transluminal trabeculotomy (GATT)
  - Visco360 (Sight Sciences, Menlo Park, CA, USA)
  - Kahook Dual Blade (New World Medical, Rancho Cucamonga, CA, USA)
  - Trabectome (NeoMedix, Tustin, CA, USA)
- Suprachoroidal devices
  - iStent Supra (Glaukos, Laguna Hills, CA, USA)
  - MINIject (iStar Medical, Wavre, Belgium)

We intend to compare interventions (with or without phacoemulsification) versus phacoemulsification alone, no surgery, another MIGS technique, trabeculectomy, or medical or laser treatment. If a study has more than one intervention group we will include the control group that is relevant to the pairwise comparison.

Types of outcome measures

Primary outcomes

- Intra- and postoperative complications that result in loss of vision. We will estimate the cumulative incidence of these AEs at longest follow-up, and categorise their severity using the glaucoma surgery-specific classification described by Sii 2018: mild (grades 1 to 3), moderate (4 to 6), and severe (7 to 10).

Secondary outcomes

Critical outcomes

- Proportion of participants who needed a secondary procedure to manage a complication
- Proportion of participants who had hypotony (early or late)
- Proportion of participants with loss of visual acuity (more than 2 Snellen lines or more than 0.3 logMAR, according to the method of recording visual acuity; or loss of light perception)
- Proportion of participants who had endophthalmitis

Important outcomes

- Proportion of participants who withdrew from the study
- Proportion of participants who withdrew from the study due to AEs
- Proportion of participants who had a spike in IOP
- Proportion of participants who had intraocular bleeding

Failure to reduce IOP will not be considered an AE. Appendix 1 summarises a list of potential complications and AEs of the interventions (ICH 2015). Studies that report no AEs will be eligible for inclusion provided the publication lists the AEs monitored.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for reports of AEs. We will use search filters for adverse effects of surgical interventions in MEDLINE and Embase as developed by Golder 2018. There will be no restrictions related to language or year of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Eyes and Vision Trials Register, in the Cochrane Library (latest issue; Appendix 2).
- MEDLINE Ovid (1946 to present; Appendix 3).
- Embase Ovid (1980 to present; Appendix 4).

- ISRCTN registry (www.isrctn.com/editAdvancedSearch; Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; Appendix 6).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp; Appendix 7).

Searching other resources

We will check the reference lists of included studies and relevant systematic reviews. We will search Retraction Watch to check if any of the included studies have been withdrawn due to error or fraud (retractiondatabase.org).

For regulatory information, we will search the following websites for publicly available clinical summary reports.

- United States Food and Drug Administration (FDA; www.fda.gov).
- European Database on Medical Devices (EUDAMED; ec.europa.eu/tools/eudamed/#/screen/home).
- The Japanese Pharmaceuticals and Medical Devices Agency (PMDA; www.pmda.go.jp/english).
- The Chinese National Medical Products Administration (NMPA; english.nmpa.gov.cn).
- The South Korean Ministry of Food and Drug Safety (MFDS; www.mfds.go.kr/eng).
- The Malaysian Medical Device Authority (MDA; portal.mda.gov.my).
- The Indian Central Drugs Standard Control Organization (CDSCO; cdsco.gov.in).
- The Israeli Ministry of Health – Medical Device Division (www.gov.il/en/departments/ministry_of_health).
- The Australian Therapeutic Goods Administration (TGA; www.tga.gov.au).
- The New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE; www.medsafe.govt.nz).

Data collection and analysis

Selection of studies

Two review authors will independently screen the titles, abstracts, and full reports resulting from the searches against the eligibility criteria using web-based software (Covidence). Clinical study reports are available after registration with the FDA. We will resolve any discrepancies by discussion. We will document the excluded studies and reasons for exclusion.

For potentially eligible studies identified through trials registers:

- if the study ended more than two years previously, we will look for publications of the study and contact the investigators if necessary to obtain published or unpublished data. If eligible, we will include the study in the review irrespective of whether we can identify a publication; and
- if the study ended within the previous two years, or is ongoing, we will document the study in the ongoing studies section.

Data extraction and management

We will extract data using a modified CONSORT statement-based extraction template (see Appendix 8; Ioannidis 2004). This template is designed to assemble a concise version of clinical study reports, including all important methods and all relevant outcomes. It includes the information normally found in a published trial report but provides greater detail.

If we identify several reports for a particular study, the primary data source will be the clinical study report.

Two review authors will independently extract data from the included studies, resolving any disagreements by discussion or by consulting a third review author.

We will report the results of the review by completing the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) harms checklist (Zorzela 2016).

Assessment of risk of bias in included studies

Two review authors (CH, CEHF) will independently assess risk of bias in duplicate. For RCTs, we will use the Cochrane risk of bias tool for randomised trials (RoB 2; Sterne 2019). We are interested in the effect of adhering to the interventions as specified in the trial protocol (the 'per-protocol' effect). We will resolve disagreements by discussion with a third review author (AA-B). We will specifically consider and report on the following sources of bias for the primary outcome at final follow-up.

- Selection bias (random sequence generation; allocation concealment): was the sequence of allocation generated using a random procedure and was the allocation concealed to people recruiting/enroling participants and to participants?
- Performance bias (masking of participants and researchers): were the recipients of care unaware of their assigned intervention? Were persons providing care unaware of the assigned intervention?
- Detection bias (masking of outcome assessors): were persons evaluating outcomes unaware of the assigned intervention?
- Attrition bias: were the rates of follow-up and compliance similar in the groups? Was the analysis by intention to treat and were there any post-randomisation exclusions?
- Selective outcome reporting bias: is there any evidence that the outcomes that were measured have not been reported?

We will grade each domain as low risk of bias, high risk of bias, or some concerns (lack of information or uncertainty of potential for bias), and we will establish overall risk of bias using the signalling questions and the RoB 2 algorithms.

For non-randomised comparative studies, two review authors (CH, CEHF) will independently assess the risk of bias using the Cochrane risk of bias tool for non-randomised studies of interventions (ROBINS-I; Sterne 2016). We are interested in the per-protocol effect. For the primary outcome at final follow-up, we will specifically consider and report on bias:

- due to confounding;
- in selection of participants;
- in classification of interventions;
- due to deviations from intended interventions;
- due to missing data;
- in measurement of outcomes; and
- due to selective reporting.

Potential confounders include age, concomitant cataract surgery, surgical/laser/medical treatment for glaucoma, high preoperative IOP, and preoperative preservative exposure. Possible cointerventions that could differ between the intervention groups and could affect outcomes are cataract surgery and other MIGS procedures. We will answer the ROBINS-I signalling questions with the following options for a domain-level risk of bias judgement: 'low', 'moderate', 'serious' or 'critical' risk of bias, or 'no information'. The overall risk of bias judgement for each outcome across all domains will feed into the GRADE assessment.

To further analyse outcome reporting bias for harms, we will use the Outcome Reporting Bias in Trials (ORBIT) tool (Appendix 9). We will generate an ORBIT matrix to show the outcomes that are reported, partially reported, or missing for each included study (ctrc.liv.ac.uk/orbit/). To assess reporting bias of harms outcomes, we will use the ORBIT classification system (Kirkham 2010). We will refer to the *Cochrane Handbook for Systematic Reviews of Interventions* to assess bias in different types of non-randomised studies of interventions (e.g. uncontrolled before-after studies, controlled before-after studies, or observational follow-up studies; Higgins 2022). We will use the web application robvis (Risk-Of-Bias VISualization) to create risk of bias plots (McGuinness 2020).

If any of the review authors is credited as author or co-author of a study, they will not be involved in the bias assessment for their work.

Measures of treatment effect

We will compare outcome data between groups using risk ratios (RRs) with their 95% confidence intervals (CIs). When studies report no events in a treatment or control arm, we will use a classic half-integer continuity correction to calculate the relative risk.

Unit of analysis issues

We anticipate having to deal with unit of analysis issues, as participants may experience more than one AE. Therefore, we will collect both the number of participants experiencing an AE and the number of AEs as separate units of analysis.

Dealing with missing data

We will conduct a per-protocol analysis.

We will include studies reporting no AEs if predefined AEs are described in their protocol or methods.

We will adjust harms effect estimates using the Copas method (Copas 2019). Copas statistical adjustment considers the relative sample size of the studies with missing outcome data and directly models the mechanism of outcome reporting bias for benefits and harms outcomes. This method uses high and low risk of bias classifications assigned using the ORBIT tool. Through the ORBIT website, Copas adjustment can be made on binary fixed-effect meta-analysis (ORBIT 2022).

Assessment of heterogeneity

We will examine the overall characteristics of the studies, in particular the type of participants and types of interventions, to assess whether they are similar enough to justify pooling results. We will examine the forest plots to assess consistency amongst the studies, focusing on the size and direction of effect in particular. We will calculate the I^2 statistic (the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error), considering I^2 values over 50% to indicate substantial inconsistency (Deeks 2020). We will also consider the Chi^2 P value, considering a value below 0.1 as indicative of statistical significance, as this estimate may have low power where a meta-analysis includes few studies.

We will interpret I^2 values as follows.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We will use the RoB 2 and ORBIT assessment tools to investigate selective or incomplete reporting. If we include 10 or more published trials in a meta-analysis, we will construct funnel plots and consider tests for asymmetry to assess publication bias, as recommended in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2022). Where appropriate, we will perform statistical tests for funnel plot asymmetry (Egger's test, Harbord's test; Egger 1997; Harbord 2006).

Data synthesis

For direct treatment comparisons, we will perform conventional pairwise meta-analyses for each primary outcome using Review Manager Web (RevMan Web; Review Manager 2022). Primary analysis will include all eligible studies. Where there are discrepancies between published and unpublished reports of the same trials, we will include only those trials for which we have unabridged clinical study reports (e.g. with consecutively numbered pages) in the primary data analysis. We will not combine data from RCTs and NRSIs. We will describe frequencies of AEs from NRSIs descriptively, using visualisations where appropriate. If both unadjusted and adjusted intervention effects are reported, we will collect unadjusted effects.

Effect sizes will be expressed risk ratios (RRs) for dichotomous data with 95% CIs. For the statistical analyses we will use the random-effects model if the comparison includes three or more trials, and the fixed-effect model if it includes fewer than three trials. If inconsistency between individual study results is considered great enough to invalidate pooling the results (e.g. the effects are in different directions, or the I^2 statistic is greater than 50% and the Chi^2 P value is below 0.1), we will not pool the data but will describe the pattern of the individual study results in a narrative synthesis and tabulated summary of the data. We may pool the data regardless of statistical heterogeneity if all the effect estimates are in the same direction and we consider a pooled estimate could provide a good summary of the individual trial results.

Subgroup analysis and investigation of heterogeneity

We will explore the possible sources of any statistical heterogeneity by conducting subgroup analyses for both AEs and SAEs, provided each subgroup contains at least two studies. Possible subgroups include:

- different intervention types (e.g. ab externo bleb-forming procedures, trabecular meshwork bypass surgery, trabecular excision/cutting procedures);
- intervention alone or in combination with phacoemulsification (single versus combination);
- pivotal trials (that led to device approval) versus published trials that were not used to obtain approval status.

We will use a formal statistical approach in RevMan Web to analyse differences amongst subgroups (Review Manager 2022).

Sensitivity analysis

We will conduct sensitivity analyses to test decisions made regarding studies at high risk of bias for an outcome in one or more key domains. Where possible, we will also perform the following sensitivity analyses for each primary outcome.

- Inclusion of only trials with low risk of attrition bias.
- Inclusion of trials with a total sample size of 50 or more randomised participants, to detect potential small-study effects.
- Inclusion of mixed types of glaucoma in study population.

Summary of findings and assessment of the certainty of the evidence

Two review authors (CH, CEHF) will use the GRADE approach to independently rate the certainty of the evidence for each outcome as high, moderate, low, or very low, based on risk of bias, inconsistency, imprecision of effect estimates, and publication bias (Schünemann 2020). In case of disagreement, a third review author (AA-B) will arbitrate. The initial level of certainty for evidence from RCTs will be high, but can be downgraded by one level for serious study limitations, or by two levels for very serious study limitations. For comparative non-randomised studies, the level of certainty will start at low and the criteria for downgrading will be the same.

We will present the main results of this review in summary of findings tables created using the GRADEpro software (GRADEpro GDT), according to recommendations provided in *Chapter 14 of the Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020). We will provide estimates derived from the meta-analysis in accordance with the GRADE methods.

We will generate one summary of findings table for each comparison, including the following outcomes measured at three months and at end of follow-up.

- Proportion of participants who had any AE that resulted in vision loss.
- Proportion of participants who needed a secondary procedure to manage a complication
- Proportion of participants who had hypotony (early or late)
- Proportion of participants with loss of visual acuity (more than 2 Snellen lines or more than 0.3 logMAR, according to the method of recording visual acuity; or loss of light perception)
- Proportion of participants who had endophthalmitis
- Proportion of participants who had a spike in IOP
- Proportion of participants who had intraocular bleeding

Where we find both RCT and NSRI data for the same outcome, we will present the two data types on separate rows.

ACKNOWLEDGEMENTS

Cochrane Eyes and Vision (CEV) will create and execute the electronic searches. We thank Anupa Shah, Managing Editor for CEV for her assistance with the editorial process. We thank the following peer reviewers for their comments on the protocol.

- Henny JM Beckers, MD, PhD, Professor of Ophthalmology and head of the glaucoma clinic, University Eye Clinic, Maastricht University Medical Center+, the Netherlands.
- Robin Featherstone, Cochrane Central Editorial Service.
- Prof Gus Gazzard, UCL and Moorfields.
- Nuala Livingstone, Cochrane Evidence Production and Methods Directorate.

Jennifer Evans (Co-ordinating Editor) and Manuele Michelessi (Editor) signed off the protocol for publication.

REFERENCES

Additional references

AGIS7 2000

The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *American Journal of Ophthalmology* 2000;**130**(4):429-40. [DOI: doi: 10.1016/s0002-9394(00)00538-9]

Copas 2019

Copas J, Marson A, Williamson P, Kirkham J. Model-based sensitivity analysis for outcome reporting bias in the meta analysis of benefit and harm outcomes. *Statistical Methods in Medical Research* 2019;**28**(3):889-903.

Covidence [Computer program]

Veritas Health Innovation Covidence. Melbourne, Australia: Veritas Health Innovation, accessed 10 May 2022. Available at www.covidence.org.

Deeks 2020

Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from training.cochrane.org/handbook/archive/v6.1.

Egger 1997

Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

FDA 2015

US Food and Drug Administration. Premarket studies of implantable minimally invasive glaucoma surgical (MIGS) devices. www.fda.gov/media/90950/download (accessed 20 July 2022).

FDA 2018

US Food and Drug Administration. Classify Your Medical Device. www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device (accessed 20 July 2022).

FDA 2022

US Food and Drug Administration. CFR – Code of Federal Regulations Title 21. Part 803: Medical Device Reporting. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=803 (accessed 20 July 2022).

Fujita 2022

Fujita A, Hashimoto Y, Matsui H, Yasunaga H, Aihara M. Recent trends in glaucoma surgery: a nationwide database study in Japan, 2011–2019. *Japanese Journal of Ophthalmology* 2022;**66**(2):183-92. [DOI: doi: 10.1007/s10384-021-00898-6]

Garway-Heath 2015

Garway-Heath DF, Crabb DP, Bunce C, Lascaratos G, Amalfitano F, Anand N, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet* 2015;**385**(9975):1295-304.

Golder 2018

Golder S, Wright K, Loke YK. The development of search filters for adverse effects of surgical interventions in medline and Embase. *Health Information and Libraries Journal* 2018;**35**(2):121-9.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), accessed 3 March 2020. Available at gradepro.org.

Harbord 2006

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20):3443-57.

Heijl 2002

Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, et al. Reduction of intraocular pressure and glaucoma progression. *Archives of Ophthalmology* 2002;**120**(10):1268-79.

Higgins 2022

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Hu 2022

Hu K, Shah A, Virgili G, Bunce C, Gazzard G. Ab interno trabecular bypass surgery with Trabectome for open-angle glaucoma. *Cochrane Database of Systematic Reviews* 2022, Issue 2. Art. No: CD011693. [DOI: 10.1002/14651858.CD011693.pub3]

ICH 2015

Introductory Guide MedDRA Version 18.0. admin.meddra.org/sites/default/files/guidance/file/intguide_18_0_english.pdf (accessed 20 July 2022).

Ioannidis 2004

Ioannidis JP, Evans SJ, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of Internal Medicine* 2004;**141**(10):781-8.

Jampel 2009

Jampel HD. Reporting post-operative complications in glaucoma surgical trials. In: Shaarawy T, Grehn F, Sherwood M, editors(s). WGA Guidelines on Design and Reporting of Glaucoma Surgical Trials. 1st edition. The Hague: Kugler Publications, 2009:33-40.

Jefferson 2014

Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, et al. Neuraminidase inhibitors for preventing

and treating influenza in adults and children. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No: CD008965. [DOI: 10.1002/14651858.CD008965.pub4]

Kass 2002

Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Archives of Ophthalmology* 2002;**120**(6):701-13.

King 2018

King AJ, Shah A, Nikita E, Hu K, Mulvaney CA, Stead R, et al. Subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma. *Cochrane Database of Systematic Reviews* 2018, Issue 12. Art. No: CD012742. [DOI: 10.1002/14651858.CD012742.pub2]

Kirkham 2010

Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;**340**:c365. [DOI: doi: 10.1136/bmj.c365.]

Le 2019

Le JT, Bicket AK, Wang L, Li T. Ab interno trabecular bypass surgery with iStent for open-angle glaucoma. *Cochrane Database of Systematic Reviews* 2019, Issue 3. Art. No: CD012743. [DOI: 10.1002/14651858.CD012743.pub2]

Luebke 2021

Luebke J, Boehringer D, Anton A, Daniel M, Reinhard T, Lang S. Trends in surgical glaucoma treatment in Germany between 2006 and 2018. *Clinical Epidemiology* 2021;**13**:581-92. [DOI: doi: 10.2147/CLEP.S310542]

Mathew 2019

Mathew DJ, McKay BR, Basilious A, Belkin A, Trope GE, Buys YM. Adherence to world glaucoma association guidelines for surgical trials in the era of microinvasive glaucoma surgeries. *Ophthalmology Glaucoma* 2019;**2**(2):78-85.

McGuinness 2020

McGuinness LA, Higgins JP. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods* 2020;**12**(1):1-7.

McLean 2019

McLean K, Myneni J, Stewart RM, Kaye SB. Ophthalmic devices and products – MHRA yellow card reporting. www.rcophth.ac.uk/wp-content/uploads/2021/01/College-News-FOCUS_January2019.pdf 2019.

Murphy 2015

Murphy C, Ogston S, Cobb C, MacEwen C. Recent trends in glaucoma surgery in Scotland, England and Wales. *British Journal of Ophthalmology* 2015;**99**(3):308-12. [DOI: doi: 10.1136/bjophthalmol-2013-304465.]

ORBIT 2022

Copas Adjustment Method. outcome-reporting-bias.org/Home/Copas (accessed 20 July 2022).

Otarola 2020

Otarola F, Virgili G, Shah A, Hu K, Bunce C, Gazzard G. Ab interno trabecular bypass surgery with Schlemm's canal microstent (Hydrus) for open angle glaucoma. *Cochrane Database of Systematic Reviews* 2020, Issue 3. Art. No: CD012740. [DOI: 10.1002/14651858.CD012740.pub2]

Page 2022

Page MJ, Higgins JP, Sterne JA. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Pitrou 2009

Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. *Archives of Internal Medicine* 2009;**169**(19):1756-61.

Review Manager 2022 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 4.12.0. The Cochrane Collaboration, 2022. Available at revman.cochrane.org.

Sandhu 2021

Sandhu A, Jayaram H, Hu K, Bunce C, Gazzard G. Ab interno supraciliary microstent surgery for open-angle glaucoma. *Cochrane Database of Systematic Reviews* 2021, Issue 5. Art. No: CD012802. [DOI: 10.1002/14651858.CD012802.pub2]

Schünemann 2020

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from training.cochrane.org/handbook/archive/v6.1.

Sii 2018

Sii S, Barton K, Pasquale LR, Yamamoto T, King AJ, Azuara-Blanco A. Reporting harm in glaucoma surgical trials: systematic review and a consensus-derived new classification system. *American Journal of Ophthalmology* 2018;**194**:153-62.

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

Sterne 2019

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

Tóth 2019

Tóth M, Shah A, Hu K, Bunce C, Gazzard G. Endoscopic cyclophotocoagulation (ECP) for open angle glaucoma and primary angle closure. *Cochrane Database of Systematic Reviews* 2019, Issue 2. Art. No: CD012741. [DOI: 10.1002/14651858.CD012741.pub2]

Weinreb 2014

Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA* 2014;**311**(18):1901-11. [DOI: doi: 10.1001/jama.2014.3192]

Yang 2021

Yang SA, Mitchell W, Hall N, Elze T, Lorch AC, Miller JW, et al, IRIS® Registry Data Analytics Consortium. Trends and usage patterns of minimally invasive glaucoma surgery in the United States: IRIS® Registry Analysis 2013–2018. *Ophthalmology Glaucoma* 2021;**4**(6):558-68. [DOI: doi: 10.1016/j.ogla.2021.03.012]

Zorzela 2016

Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 2016;**352**:i157.

APPENDICES

Appendix 1. List of potential harms of minimally invasive glaucoma surgery

Preoperative adverse events

- Anaesthetic complication
- Device malfunction prior to implantation or during procedure

Intraoperative adverse events

- Device malfunction identified prior to implantation
- Inadvertent perforation of sclera
- Hyphaema
- Inadvertent loss of vitreous
- Choroidal haemorrhage or effusion

Postoperative adverse events

- Flat anterior chamber (central lens, corneal touch)
- Visual acuity loss (loss of 2 Snellen lines or more, or loss of light perception: no light perception is always reportable; beyond 20/400, the increments corresponding to 1 line are as follows: 5/200, 2/200, 1/200, hand movement, and light perception)
- Tube malposition (corneal touch, lenticular, anterior capsule laceration, iris/vitreous/other occlusion, tube retraction, exposure (transconjunctival)
- Device malfunction (including presumed tube compression/kink)
- Tube insertion within choroid (for pars plana)
- Tube or flow restrictor obstruction by iris, vitreous, lens, fibrous overgrowth, fibrin, blood, etc.
- Unintended implant exposure (including tube)
- Dysaesthesia (with or without large or exposed bleb, dellen)
- Wound dehiscence (persistent aqueous leak or fistula formation, requiring or not requiring treatment or surgery)
- Inflammation (persistent at six months and non-pre-existing anterior or posterior uveitis in same or fellow eye, sterile hypopyon, or pupillary membrane formation)
- Infection (localised to area of device or endophthalmitis)
- Bleeding (vitreous haemorrhage or persistent and non-pre-existing hyphaema)
- Peripheral anterior synechia
- Corneal complications (corneal oedema, Descemet's membrane detachment, rupture of trabeculo-Descemet's membrane, opacification, or graft decompensation)
- Cataract (formation or progression)
- Retinal complications (dialysis, flap tears, retinal detachment, or proliferative vitreoretinopathy, requiring or not requiring surgery)
- Choroidal complications (massive choroidal haemorrhage)
- Scleral ectasia
- Strabismus (any new restriction of ocular movement or secondary diplopia)
- Unplanned surgical reintervention
- Loss of eye
- Chronic pain

- Ptosis
- Atrophy/phthisis
- Systemic complications

Additional potential late events (more than five years after intervention)

- Device removal and reasons for removal
- Secondary surgery/procedure to lower intraocular pressure (unplanned intervention)
- At least 30% reduction in endothelial cell density, with or without corneal decompensation, requiring or not requiring corneal surgery
- Late wound leak
- Bleb-related infection/endophthalmitis

Definitions

- Serious adverse event (SAE): an adverse event that results in death; is life-threatening; requires subject hospitalisation or prolongation of existing hospitalisation; or results in persistent or significant disability such as visual loss
- Intraoperative: occurring during a surgical procedure
- Early: occurring within first postoperative month
- Late: occurring after one month
- Persistent: persisting for longer than three months
- Investigators can assess the intensity of an adverse event as follows.
  - Mild: temporary event that is tolerated well and does not interfere with normal daily activities
  - Moderate: event that results in discomfort and impairs normal activity
  - Severe: event that results in substantial impairment of normal activities
- Hypotony should be classified as an early adverse event (within two weeks after surgery) or a late adverse event (more than two weeks after surgery) if it occurs with at least one of the following conditions.
  - Flat anterior chamber requiring anterior chamber reformation
  - Corneal folds
  - Choroidal effusions requiring or undergoing surgical drainage
  - Suprachoroidal haemorrhage
  - Maculopathy
  - Corneal astigmatism
  - Disc swelling
- Chronic anterior uveitis should be defined as inflammation of grade 1 or worse that persists for more than three months postoperatively or that recurs less than three months after discontinuing treatment, and that:
  - results in a decrease of 2 lines or more in best-corrected visual acuity (BCVA);
  - requires aspirate for diagnosis;
  - requires topical corticosteroids; or
  - requires systemic or periocular/intraocular steroids.
- Intraocular bleeding should be defined as:
  - layered hyphaema covering or not covering the pupil;
  - blood occluding internal fistula or stent; or
  - circulating blood in the anterior chamber or vitreous cavity that decreases vision.

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Glaucoma, Open-Angle] explode all trees
#2 MeSH descriptor: [Intraocular Pressure] this term only
#3 MeSH descriptor: [Ocular Hypertension] explode all trees
#4 OAG or POAG or IOP or OHT
#5 simple near/3 glaucoma*
#6 open near/2 angle near/2 glaucoma*
#7 primary near/2 glaucoma*
#8 chronic near/2 glaucoma*
#9 secondary near/2 glaucoma*
#10 low near/2 tension near/2 glaucoma*
#11 low near/2 pressure near/2 glaucoma*
#12 normal near/2 tension near/2 glaucoma*

#13 normal near/2 pressure near/2 glaucoma*
#14 pigment near/2 glaucoma*
#15 MeSH descriptor: [Exfoliation Syndrome] this term only
#16 exfoliat* near/2 syndrome*
#17 exfoliat* near/2 glaucoma*
#18 pseudoexfoliat* near/2 syndrome*
#19 pseudoexfoliat* near/2 glaucoma*
#20 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21 trabectome
#22 Ab interno NEAR/2 (trabeculectomy or trabeculotomy)
#23 trabecular NEAR/2 bypass*
#24 #21 or #22 or #23
#25 MeSH descriptor: [Stents] explode all trees
#26 Schlemm* NEAR/4 (stent* or microstent* or scaffold*)
#27 Hydrus
#28 (micro-bypass* or microbypass* or micro* or bypass*) NEAR/2 stent*
#29 bypass NEAR/3 (trabecul* or interno)
#30 #25 or #26 or #27 or #28 or #29
#31 MeSH descriptor: [Endoscopy] this term only
#32 MeSH descriptor: [Lasers, Semiconductor] explode all trees
#33 MeSH descriptor: [Light Coagulation] this term only
#34 MeSH descriptor: [Laser Coagulation] explode all trees
#35 endoscop* near/2 (cyclophotocoagulat* or cyclo-photocoagulat*)
#36 ECP
#37 cycloablat*
#38 #31 or #32 or #33 or #34 or #35 or #36 or #37
#39 Xen or Xen45 or Xen63 or Xen140
#40 gel* near/3 (microstent* or stent* or implant*)
#41 AqueSys
#42 poly styrene-block-isobutylene-block-styrene
#43 implant* near/2 (ab interno or ab externo)
#44 InnFocus or MicroShunt* or PreserFLo*
#45 #39 or #40 or #41 or #42 or #43 or #44
#46 istent*
#47 (micro-bypass* or microbypass* or micro* or bypass*) near/2 stent*
#48 bypass near/3 (trabecul* or interno)
#49 Cypass*
#50 MINIject
#51 #46 or #47 or #48 or #49 or #50
#52 (micro-bypass* or microbypass* or micro* or bypass*) near/2 stent*
#53 bypass near/3 (trabecul* or interno)
#54 (supraciliary or Suprachoroidal) near/3 (microstent* or micro stent* or implant* or drainage or device*)
#55 Gold Micro Shunt or SOLX Gold Shunt or iStent Supra or Cypass or Aquashunt or STARflo or Esnoper
#56 #52 or #53 or #54 or #55
#57 ab interno trabeculectomy or trabeculectomy ab interno
#58 ab interno trabeculotomy or trabeculotomy ab interno
#59 ab interno goniotrabeculotomy or goniotrabeculotomy ab interno
#60 ab interno canaloplasty or canaloplasty ab interno or AbiC
#61 trabecular near/2 bypass*
#62 trabectome
#63 goniotom*
#64 trabecular near/3 (ablat* or incis* or excis*)
#65 Kahook Dual Blade or KDB
#66 gonioscop* near/2 assist* near/2 transluminal or GATT
#67 OMNI or iTrack
#68 #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67
#69 (laser* or frequenc* or deep) near/2 (sclerotom* or sclerectom*)
#70 Visco360
#71 #69 or #70
#72 #24 or #30 or #38 or #45 or #51 or #56 or #68 or #71
#73 #20 and #72
#74 complication*

#75 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE]
#76 safe*
#77 MeSH descriptor: [] explode all trees and with qualifier(s): [complications - CO]
#78 MeSH descriptor: [Postoperative Complications] this term only
#79 #74 or #75 or #76 or #77 or #78
#80 #73 and #79

Appendix 3. MEDLINE Ovid search strategy

1. exp glaucoma open angle/
2. exp intraocular pressure/
3. ocular hypertension/
4. (OAG or POAG or IOP or OHT).tw.
5. (simple$ adj3 glaucoma$).tw.
6. (open adj2 angle adj2 glaucoma$).tw.
7. (primary adj2 glaucoma$).tw.
8. (chronic adj2 glaucoma$).tw.
9. (secondary adj2 glaucoma$).tw.
10. (low adj2 tension adj2 glaucoma$).tw.
11. (low adj2 pressure adj2 glaucoma$).tw.
12. (normal adj2 tension adj2 glaucoma$).tw.
13. (normal adj2 pressure adj2 glaucoma$).tw.
14. (pigment$ adj2 glaucoma$).tw.
15. exfoliation syndrome/
16. (exfoliat$ adj2 syndrome$).tw.
17. (exfoliat$ adj2 glaucoma$).tw.
18. (pseudoexfoliat$ adj2 syndrome$).tw.
19. (pseudoexfoliat$ adj2 glaucoma$).tw.
20. or/1-19
21. trabectome.tw.
22. (Ab interno adj2 (trabeculectomy or trabeculotomy)).tw.
23. (trabecular adj2 bypass$).tw.
24. or/21-23
25. exp Stents/
26. (Schlemm$ adj4 (stent$ or microstent$ or scaffold$)).tw.
27. Hydrus.tw.
28. ((micro-bypass$ or microbypass$ or micro$ or bypass$) adj2 stent$).tw.
29. (bypass adj3 (trabecul$ or interno)).tw.
30. or/25-29
31. Endoscopy/
32. Lasers, Semiconductor/
33. light coagulation/
34. laser coagulation/
35. (endoscop$ adj2 (cyclophotocoagulat$ or cyclo-photocoagulat$)).tw.
36. ECP.tw.
37. cycloablat$.tw.
38. or/31-37
39. (Xen or Xen45 or Xen63 or Xen140).tw.
40. (gel$ adj3 (microstent$ or stent$ or implant$)).tw.
41. AqueSys.tw.
42. poly styrene-block-isobutylene-block-styrene.tw.
43. (implant$ adj2 (ab interno or ab externo)).tw.
44. (InnFocus or MicroShunt$ or PreserFLo$).tw.
45. or/39-44
46. istent$.tw.
47. ((micro-bypass$ or microbypass$ or micro$ or bypass$) adj2 stent$).tw.
48. (bypass adj3 (trabecul$ or interno)).tw.
49. Cypass$.tw.
50. MINIject.tw.
51. or/46-50
52. ((micro-bypass$ or microbypass$ or micro$ or bypass$) adj2 stent$).tw.
53. (bypass adj3 (trabecul$ or interno)).tw.

54. ((supraciliary or Suprachoroidal) adj3 (microstent$ or micro stent$ or implant$ or drainage or device$)).tw.
55. (Gold Micro Shunt or SOLX Gold Shunt or iStent Supra or Cypass or Aquashunt or STARflo or Esnoper).tw.
56. or/52-55
57. (Ab interno adj3 (trabeculectom$ or trabeculotom$ or canaloplast$ or oniotrabeculotom$)).tw.
58. goniotom$.tw.
59. (trabecular adj3 (ablat$ or incis$ or excis$)).tw.
60. (Kahook Dual Blade or KDB).tw.
61. (gonioscop$ adj2 assist$ adj2 transluminal).tw.
62. GATT.tw.
63. (OMNI or iTrack).tw.
64. or/57-63
65. ((laser$ or frequenc$ or deep) adj2 (sclerotom$ or sclerectom$)).tw.
66. Visco360.tw.
67. or/65-66
68. 24 or 30 or 38 or 45 or 51 or 56 or 64 or 67
69. 20 and 68
70. complication*.ti,ab.
71. ae.fs.
72. safe*.ti,ab.
73. co.fs.
74. Postoperative Complications/
75. or/70-74
76. 69 and 75

Appendix 4. Embase Ovid search strategy

1. open angle glaucoma/
2. intraocular pressure/
3. intraocular hypertension/
4. (OAG or POAG or IOP or OHT).tw.
5. (open adj2 angle adj2 glaucoma$).tw.
6. (primary adj2 glaucoma$).tw.
7. (chronic adj2 glaucoma$).tw.
8. (secondary adj2 glaucoma$).tw.
9. (low adj2 tension adj2 glaucoma$).tw.
10. (low adj2 pressure adj2 glaucoma$).tw.
11. (normal adj2 tension adj2 glaucoma$).tw.
12. (normal adj2 pressure adj2 glaucoma$).tw.
13. (pigment$ adj2 glaucoma$).tw.
14. exfoliation syndrome/
15. (exfoliat$ adj2 syndrome$).tw.
16. (exfoliat$ adj2 glaucoma$).tw.
17. (pseudoexfoliat$ adj2 syndrome$).tw.
18. (pseudoexfoliat$ adj2 glaucoma$).tw.
19. or/1-18
20. trabectome.tw.
21. (ab interno adj2 (trabeculectomy or trabeculotomy)).tw.
22. (trabecular adj2 bypass$).tw.
23. or/20-22
24. stent/
25. (Schlemm$ adj4 (stent$ or microstent$ or scaffold$)).tw.
26. Hydrus.tw.
27. ((micro-bypass$ or microbypass$ or micro$ or bypass$) adj2 stent$).tw.
28. (bypass adj3 (trabecul$ or interno)).tw.
29. or/24-28
30. laser coagulation/
31. ophthalmic argon laser/
32. (endoscop$ adj2 cyclophotocoagulat$).tw.
33. ECP.tw.
34. cycloablat$.tw.
35. or/30-34
36. (Xen or Xen45 or Xen63 or Xen140).tw.

37. (gel$ adj3 (microstent$ or stent$ or implant$)).tw.
38. AqueSys.tw.
39. (InnFocus or MicroShunt$).tw.
40. poly styrene-block-isobutylene-block-styrene.tw.
41. (implant$ adj2 (ab interno or ab externo)).tw.
42. or/36-41
43. istent$.tw.
44. ((micro-bypass$ or micro$ or bypass$) adj2 stent$).tw.
45. (bypass adj3 (trabecul$ or interno)).tw.
46. Cypass$.tw.
47. MINIject.tw.
48. or/43-47
49. ((micro-bypass$ or micro$ or bypass$) adj2 stent$).tw.
50. (bypass adj3 (trabecul$ or interno)).tw.
51. ((supraciliary or suprachoroidal) adj3 (microstent$ or micro stent$ or implant$ or drainage or device$)).tw.
52. (Gold Micro Shunt or SOLX Gold Shunt or iStent Supra or Cypass or Aquashunt or STARflo or Esnoper).tw.
53. or/49-52
54. trabeculotomy/
55. (Ab interno adj3 (trabeculectom$ or trabeculotom$ or canaloplast$ or goniotrabeculotom$)).tw.
56. (trabecular adj2 bypass$).tw.
57. trabeculotome/
58. trabectome.tw.
59. goniotom$.tw.
60. (trabecular adj3 (ablat$ or incis$ or excis$)).tw.
61. (Kahook Dual Blade or KDB).tw.
62. (gonioscop$ adj2 assist$ adj2 transluminal).tw.
63. GATT.tw.
64. (OMNI or iTrack).tw.
65. or/54-64
66. ((laser$ or frequenc$ or deep) adj2 (sclerotom$ or sclerectom$)).tw.
67. Visco360.tw.
68. or/66-67
69. 23 or 29 or 35 or 42 or 48 or 53 or 65 or 68
70. 19 and 69
71. complication*.ti,ab.
72. co.fs.
73. safe*.ti,ab.
74. ae.fs.
75. (post adj2 operative adj2 morbidity).ti,ab.
76. surgical risk/
77. complication/
78. or/71-77
79. 70 and 78

Appendix 5. ISRCTN search strategy

(safety OR complication OR adverse) Condition: Glaucoma

Appendix 6. Clinicaltrials.gov search strategy

(Open Angle Glaucoma OR intraocular pressure) AND (stent OR istent OR trabectome OR Ab interno OR ab externo OR cyclophotocoagulation OR microbypass OR Kahook) AND (safety OR complication OR adverse)

Appendix 7. WHO ICTRP search strategy

Title: safety OR complication OR adverse
AND
Condition: Open Angle Glaucoma OR intraocular pressure
Intervention stent OR istent OR trabectome OR Ab interno OR ab externo OR cyclophotocoagulation OR microbypass OR Kahook
AND
Disease: stent OR istent OR trabectome OR Ab interno OR ab externo OR cyclophotocoagulation OR microbypass OR Kahook

Appendix 8. Modified CONSORT Harms Statement for clinical study reports of non-pharmacologic treatment interventions

We will extract the following for each trial.

- Background and objectives.
- Methods, including trial design and important changes to methods after trial commencement (e.g. eligibility criteria), with reasons.
- Participants, including eligibility criteria for participants, and settings and locations of data collection.
- Interventions for each group with sufficient detail to enable replication, including time and method of administration.
- Outcomes: prespecified primary and secondary outcome measures, including time and method of assessment and changes to trial outcomes after trial commencement, with reasons.
- Sample size: calculation method and explanation of any interim analyses and stopping guidelines.
- Randomisation, including method for generating the random allocation sequence.
- Blinding (masking): type and methods of masking.
- Statistical methods used to compare groups for primary and secondary outcomes and for additional analyses (e.g. subgroup analyses and adjusted analyses).
- Participant flow, numbers of participants randomly assigned, and losses and exclusions after randomisation, with reasons.
- Baseline demographic and clinical characteristics for each group.
- Participant withdrawals due to harms and participant experiences with the allocated treatment.
- Primary and secondary outcome results for each group.
- Ancillary analyses: results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory.
- All important harms or unintended effects in each group.
- Denominators for analyses on harms.
- Absolute risk of harms per arm and per adverse event type, grade, and seriousness, with appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent.
- Any subgroup analyses and exploratory analyses for harms.

Appendix 9. Outcome Reporting Bias in Trials (ORBIT) tool

ORBIT II classification system for missing or complete outcome reporting in harm outcomes

Classification	Description	Level of reporting	Risk of bias*
Explicit specific harm outcome: measured and compared across treatment groups			
P1	States outcome analysed but reported only that P value > 0.05	Partial	High risk
P2	States outcome analysed but reported only that P value < 0.05	Partial	High risk
P3	Insufficient reporting for meta-analysis or full tabulation	Partial	Low risk
Explicit specific harm outcome: measured but not compared across treatment groups			
Q	Clear that outcome was measured and clear outcome was not compared	NA	No risk
Explicit specific harm outcome: measured, not clear whether compared or not across treatment groups			
R1	Clear that outcome was measured but no results reported	None	High risk
R2	Result reported globally across all groups	None	High risk
R3	Result reported from some groups only	None	High risk

(Continued)

Specific harm outcome not explicitly mentioned: clinical judgement says likelymeasured and likely compared across treatment groups			
S1	Only pooled adverse events reported (could include specific harm outcome)	None	High risk
S2	No harms mentioned or reported	None	High risk
Specific harm outcome not explicitly mentioned: clinical judgement says likely measured but no events			
T1	Specific harm not mentioned but all other specific harms fully reported	None	Low risk
T2	No description of specific harms	None	Low risk
Specific harm outcome not explicitly mentioned, clinical judgement says unlikely measured			
U	No harms mentioned or reported	None	Low risk
Explicit the specific harm outcome was not measured			
V	Report clearly specifies that data on the specific harm of interest were not measured	NA	No risk

*Bias would occur if specific harm had been measured, but data were presented or suppressed in a way that would mask the harm profile of particular interventions.

NA: not applicable.

CONTRIBUTIONS OF AUTHORS

CH conceived the idea for the review and drafted the protocol. CEHF, GV, PTK and AA-B reviewed and edited subsequent drafts.

DECLARATIONS OF INTEREST

CH: none
CEHF: none
GV: none
PTK: is an independent contractor for Santen and Glaukos Corporation
AA-B: none

SOURCES OF SUPPORT

Internal sources

- Glaucoma UK, UK

  CH is supported by Glaucoma UK award 2021
- NIHR, UK

  CH receives support from the National Institute for Health Research CL 2020-18-009

External sources

- Public Health Agency, UK

  The HSC Research and Development (R&D) Division of the Public Health Agency funds the Cochrane Eyes and Vision editorial base at Queen's University Belfast.
- Queen's University Belfast, UK

Gianni Virgili, Co-ordinating Editor for Cochrane Eyes and Vision's work is funded by the Centre for Public Health, Queen's University of Belfast, Northern Ireland.