



**QUEEN'S
UNIVERSITY
BELFAST**

Subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma

King, A. J., Shah, A., Nikita, E., Hu, K., Mulvaney, C. A., Stead, R., & Azuara-Blanco, A. (2018). Subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma. *Cochrane Database of Systematic Reviews*, 2018(12), Article CD012742. <https://doi.org/10.1002/14651858.CD012742.pub2>

Published in:
Cochrane Database of Systematic Reviews

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights
Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. This work is made available online in accordance with the publisher's policies. Please refer to any applicable terms of use of the publisher.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Open Access
This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. – Share your feedback with us: <http://go.qub.ac.uk/oa-feedback>



Cochrane
Library

Cochrane Database of Systematic Reviews

Subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma (Review)

King AJ, Shah A, Nikita E, Hu K, Mulvaney CA, Stead R, Azuara-Blanco A

King AJ, Shah A, Nikita E, Hu K, Mulvaney CA, Stead R, Azuara-Blanco A.
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](https://doi.org/10.1002/14651858.CD012742.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	6
Figure 1.	7
DISCUSSION	8
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
CHARACTERISTICS OF STUDIES	11
APPENDICES	12
CONTRIBUTIONS OF AUTHORS	15
DECLARATIONS OF INTEREST	16
SOURCES OF SUPPORT	16
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	16
INDEX TERMS	16

[Intervention Review]

Subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma

Anthony J King¹, Anupa Shah², Eleni Nikita³, Kuang Hu⁴, Caroline A Mulvaney⁵, Richard Stead¹, Augusto Azuara-Blanco⁶

¹Ophthalmology, Nottingham University Hospital, Nottingham, UK. ²Cochrane Eyes and Vision, ICEH, London School of Hygiene & Tropical Medicine, London, UK. ³Glaucoma Service, Moorfields Eye Hospital NHS Foundation Trust, London, UK. ⁴Moorfields Eye Hospital NHS Foundation Trust, London, UK. ⁵School of Medicine, University of Nottingham, Nottingham, UK. ⁶Centre for Public Health, Queen's University Belfast, Belfast, UK

Contact address: Anthony J King, Ophthalmology, Nottingham University Hospital, Derby Road, Nottingham, NG7 2UH, UK.
anthony.king@nottingham.ac.uk, anthony.king@nuh.nhs.uk.

Editorial group: Cochrane Eyes and Vision Group

Publication status and date: New, published in Issue 12, 2018.

Citation: King AJ, Shah A, Nikita E, Hu K, Mulvaney CA, Stead R, Azuara-Blanco A. 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](https://doi.org/10.1002/14651858.CD012742.pub2).

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Glaucoma is a leading cause of irreversible blindness. Subconjunctival draining minimally-invasive glaucoma devices such as the Xen gelatin implant and InnFocus stent have been introduced as a treatment to prevent glaucoma progressing.

These implants provide a channel to allow aqueous humour from the anterior chamber of the eye to drain into the subconjunctival space on the surface of the eye thus reducing intraocular pressure (IOP) and mimicking the mechanism of the most commonly undertaken glaucoma surgery, trabeculectomy.

Objectives

To evaluate the efficacy and safety of subconjunctival draining minimally-invasive glaucoma devices in treating people with open angle glaucoma and ocular hypertension whose condition is inadequately controlled with drops.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; which contains the Cochrane Eyes and Vision Trials Register; 2018, Issue 6); Ovid MEDLINE; Ovid Embase; the ISRCTN registry; ClinicalTrials.gov and the WHO ICTRP. The date of the search was 10 July 2018.

Selection criteria

We searched for randomised controlled trials (RCTs) of Xen gelatin implant or InnFocus MicroShunt to other surgical treatments (other minimally-invasive glaucoma device techniques, trabeculectomy), laser treatment or medical treatment. We also planned to include trials where these devices were combined with phacoemulsification compared to phacoemulsification alone.

Data collection and analysis

We planned to have two review authors independently extract data from reports of included studies using a data collection form and analyse data based on methods expected by Cochrane. Our primary outcome was mean change in IOP. Secondary outcomes included proportion of participants who were drop-free; proportion of participants who achieved an IOP of 21 mmHg or less, 17 mmHg or less or 14

mmHg or less; and proportion of participants experiencing intra- and postoperative complications. We planned to measure all outcomes in the short-term (six to 18 months), medium-term (18 to 36 months), and long-term (36 months onwards).

Main results

We found no completed RCTs that met our inclusion criteria. We found one ongoing study (NCT01881425). The study compares InnFocus MicroShunt to trabeculectomy in people with primary open angle glaucoma. The primary outcome is greater than 20% IOP reduction from baseline to 12 months' follow-up. A total of 889 people aged between 40 and 85 years have been enrolled. The estimated study completion date is November 2019.

Authors' conclusions

There is currently no high-quality evidence for the effects of subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled open angle glaucoma. Properly designed RCTs are needed to assess the medium- and long-term efficacy and safety of this technique.

PLAIN LANGUAGE SUMMARY

Devices that drain on to the surface of the eye beneath the surface layer to reduce eye pressure in people with or at risk of glaucoma

What was the aim of the review?

The aim of this Cochrane Review was to find out if devices draining from the front compartment of the eye (anterior chamber) onto the surface of the eye beneath the surface layer (subconjunctival space) known as minimally-invasive glaucoma devices are effective in reducing the pressure in the eye in people with glaucoma that is not adequately controlled by drops. Cochrane Review authors collected and analysed all relevant studies to answer this question and found no completed studies and one ongoing study.

Key messages

There are no relevant published studies comparing subconjunctival draining minimally-invasive glaucoma devices with other treatments.

What was studied in the review?

Glaucoma is the leading cause of irreversible blindness. In glaucoma, the optic nerve at the back of eye is damaged, in many cases because the pressure inside the eye is too high. Doctors can lower the eye pressure by surgery. Subconjunctival draining minimally-invasive glaucoma devices could help make this surgery less traumatic, which may be safer than standard surgery and more comfortable for people with a quicker visual recovery period.

What are the main results of the review?

The Cochrane Review authors did not find any completed studies that could be included in this review.

How up-to-date is the review?

The Cochrane Review authors searched for studies published up to 10 July 2018.

BACKGROUND

The protocol for this review (King 2017) was based on the protocol from the published review on ab interno trabecular bypass surgery with Trabectome for open angle glaucoma (OAG) (Hu 2016).

Description of the condition

Glaucoma is a chronic, progressive optic neuropathy, affecting up to 4% of people by the age of 80 years (Burr 2007). It is the leading cause of irreversible blindness, affecting 60 million people globally (Quigley 2006). This figure is expected to increase to 80 million people by 2020. OAG is the most common type, accounting for three-quarters of cases (Quigley 2006). In one large population cohort, one in six people with OAG became bilaterally blind (Peters 2013). The only proven way to prevent vision loss is to reduce the pressure inside the eye (intraocular pressure; IOP) over the long term (AGIS 2000; CNTG Study Group 1998; Heijl 2002; Kass 2002). Approaches to reducing IOP include medical therapy, laser treatments, and surgery. Because commercially available eye-drop preparations have a short-lasting effect, medical therapy requires eye-drops to be instilled one or more times daily for life. Adherence is very poor, even if use is monitored (Friedman 2009; Okeke 2009). Conventional surgical techniques such as trabeculectomy are associated with significant risks, with more than 40% of people developing perioperative complications (Kirwan 2013; Lichter 2001), and reoperation being needed in 7% to 18% of people (Gedde 2012; Kirwan 2013). Therefore, they are often reserved for disease that is progressing despite other treatments (King 2013).

Description of the intervention

A number of minimally-invasive glaucoma surgeries (MIGS) have been developed with the aim of achieving long-term reduction of IOP with a better safety profile than conventional surgery (Francis 2011). These include Xen gelatin ab interno implant (AqueSys Inc., Aliso Viejo, CA, USA), and InnFocus MicroShunt, ab externo implant (InnFocus Inc., Miami, FL, USA). The Xen has been approved in Europe for the treatment of glaucoma and is a CE marked treatment, but at the time of publishing this review does not have US Food and Drug Administration (FDA) approval. The latter is currently undergoing a phase 3 clinical trial to acquire FDA approval.

How the intervention might work

In people with OAG, there is increased resistance to aqueous humour outflow through the trabecular meshwork. Both the Xen and InnFocus implants bypass this resistance by creating a channel between the anterior chamber of the eye and the subconjunctival space, thus allowing aqueous to bypass the trabecular meshwork into the subconjunctival space and, thereby, reducing IOP. Both devices are routinely augmented with mitomycin-C, an antimetabolite which is injected subconjunctivally at the time of surgery to reduce postoperative scarring and reduce the risk of surgical failure.

Why it is important to do this review

The increased burden of glaucoma worldwide has generated significant interest in the development of novel surgical treatments for glaucoma. In addition, consultation with patients and healthcare professionals has identified a need for better treatments

for glaucoma (James Lind Alliance 2013). These techniques and devices embrace the common theme of being effective in reducing IOP and reducing medication burden, whilst causing minimal tissue trauma, having a very good safety profile, and reduced visual recovery time. Additionally, they have a shorter surgical time, an easily reproducible technique, and a short learning curve, which makes them accessible to all ophthalmologists who manage people with glaucoma, rather than being the territory of glaucoma specialists alone (Batlle 2016; Richter 2016). The literature suggests there is already widespread use of Xen and InnFocus implants in both Europe and the USA (Batlle 2016; Rodriguez-Una 2016; Sheybani 2015a).

Both devices may be used alone or combined with phacoemulsification (cataract surgery), a sight-restoring operation to remove the natural lens of the eye when it has lost clarity.

In view of the potential benefits for patients and the widespread uptake of the techniques, it is important to critically evaluate the evidence for the efficacy and safety of the subconjunctival draining minimally-invasive glaucoma devices when used alone and in combination with phacoemulsification cataract surgery.

As phacoemulsification itself alone is proven to reduce IOP (Mansberger 2012), it is important to establish whether undertaking phacoemulsification in combination with these microshunts is responsible for additional IOP reduction.

This Cochrane Review was conducted in parallel with other reviews currently undertaken by the Cochrane Eyes and Vision MIGS Consortium, which includes MIGS techniques and devices such as the Trabectome (NeoMedix, Tustin, CA, USA) (Hu 2016), Hydrus Schlemm's canal Microstent (Ivantis Inc., Irvine, CA, USA) (Otarola 2017), endoscopic cytophotocoagulation (Endo Optiks, Waltham, MA, USA) (Tóth 2017), and iStent and iStent inject (Glaukos Corporation, Laguna Hills, CA, USA) (Le 2017) and supraciliary microstent surgery (Sandhu 2017).

OBJECTIVES

To evaluate the efficacy and safety of subconjunctival draining minimally-invasive glaucoma devices in treating people with open angle glaucoma and ocular hypertension whose condition is inadequately controlled with drops.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomised controlled trials (RCTs) prepared in any language, irrespective of their publication status.

Types of participants

Participants had OAG of any type, including primary and secondary OAG. We excluded closed angle glaucoma. As there are no universally accepted criteria by which glaucoma may be defined, we permitted studies to use their own definitions of glaucoma. In addition, we included participants with ocular hypertension, normal tension glaucoma, or possible glaucoma (suspects for glaucoma). We did not apply any restrictions regarding location, setting, or demographic factors.

Types of interventions

The intervention was the Xen gelatin ab interno implant (AqueSys Inc., Aliso Viejo, CA, USA), or the InnFocus MicroShunt ab externo implant (InnFocus Inc., Miami, FL, USA).

The Xen Gel Implant is a 6 mm cylinder of collagen-derived gelatin, cross-linked with glutaraldehyde. It comes preloaded in an injector and is implanted ab interno, creating a drainage pathway between the anterior chamber and subconjunctival space, creating a bleb (Lewis 2014; Sheybani 2015a; Sheybani 2015b; Sheybani 2016). The procedure is routinely augmented with subconjunctival injection of mitomycin-C. The InnFocus MicroShunt Device is approximately 70 microns in diameter, with an outer diameter of 350 microns and a length of approximately 8.5 mm (Batlle 2016; Pinchuk 2015; Riss 2015). The surgical procedure involves creating a conjunctival pouch and a small scleral tunnel, through which the shunt enters the anterior chamber. The conjunctiva is sutured at the end of surgery and the aqueous humour flows through the tube in the subconjunctival area and creates a bleb. The procedure is routinely augmented with subconjunctival injection of mitomycin-C (Batlle 2016; Pinchuk 2008).

We planned to compare subconjunctival draining minimally-invasive glaucoma devices:

- in combination with phacoemulsification compared with phacoemulsification alone;
- to laser treatment (selective laser trabeculoplasty or argon laser trabeculoplasty);
- to other MIGS techniques;
- to conventional glaucoma surgery (trabeculectomy);
- to medical therapy.

Types of outcome measures

We did not use the reporting of particular outcomes as a criterion for eligibility for the review. We did not exclude studies from the review solely on the grounds of an outcome of interest not being reported.

We planned to report outcomes in the short-term (six to 18 months), medium-term (18 to 36 months), and long-term (36 months onwards).

Primary outcomes

- Mean change in IOP measured with Goldman applanation tonometry.

Several different glaucoma outcome measures have been specified as primary outcomes in other Cochrane Reviews and protocols (Ismail 2015). One study classified IOP, visual field, safety, and anatomic outcomes as being highly important to glaucoma experts (Ismail 2016). A panel of patients from the Patient and Public Involvement Group of the National Institute for Health Research (NIHR) Biomedical Research Centre for Ophthalmology identified drop-free disease control as a highly valued outcome (unpublished).

Secondary outcomes

- Proportion of participants who were drop-free (not using eye drops).

- Mean change in number of IOP-lowering drops taken per day.
- Proportion of participants who achieved an IOP of 21 mmHg or less.
- Proportion of participants who achieve an IOP of 17 mmHg or less.
- Proportion of participants who achieve an IOP of 14 mmHg or less.
- Proportion of participants who required further glaucoma surgery, including laser, as recorded by the investigators of the included trials.
- Mean change in health-related quality of life (HRQoL).

Adverse effects

- Proportion of participants experiencing intra- and postoperative complications including, but not restricted to, the following:
 - * 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);
 - * bleeding, as recorded by the investigators;
 - * endophthalmitis, as recorded by the investigators;
 - * IOP spikes (postoperative rise in IOP, measured using Goldmann applanation tonometry, of more than 10 mmHg compared to the previous assessment, including during the first postoperative month).

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 10 July 2018.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 6) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 10 July 2018) (Appendix 1).
- MEDLINE Ovid (1946 to 10 July 2018) (Appendix 2).
- Embase Ovid (1980 to 10 July 2018) (Appendix 3).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 10 July 2018) (Appendix 4).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 10 July 2018) (Appendix 5).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 10 July 2018) (Appendix 6).

Searching other resources

We searched the reference lists of included studies for other possible studies. We checked manufacturer's websites (AqueSys Inc., Aliso Viejo, CA, USA; InnFocus Inc, Miami, FL, USA) to ascertain if any new trials are being undertaken but there were no details of any new studies currently being planned or conducted. As we were not able to identify any forthcoming trials from the relevant manufacturers websites we did not contact individuals or organisations for any further follow-ups.

Data collection and analysis

Selection of studies

Three review authors (AS, EN, RS) independently screened titles and abstracts of all articles identified by the search using web-based online review management software ([Covidence](#)). If abstracts were not available, we planned to screen full-text articles. We planned to obtain full-text copies of all reports retained after this initial screening, and two review authors would have assessed them independently for inclusion in the review. If there was disagreement regarding eligibility, a third review author would have arbitrated. If any full-text reports were rejected, we planned to record the reasons for this in the 'Characteristics of excluded studies' table.

As we only found one ongoing trial and no completed RCTs for inclusion in our review, we were unable to complete the steps for data extraction or analysis. In future updates, if we find any trials that meet our inclusion criteria or if the ongoing trial is completed and results published, we will follow the process outlined below.

Data extraction and management

We will extract data from reports of included studies using a data collection form, which will be developed and piloted on the first five included studies. Two review authors will independently extract study characteristics from reports of each study and enter the data into Review Manager 5 (RevMan 5) ([Review Manager 2014](#)). If there is disagreement, a third review author will arbitrate.

Data collected in [Appendix 7](#) will be presented in the 'Characteristics of included studies' table. Where data on included studies are missing or unclear, we will contact the individuals or organisations involved to obtain clarification. We will collect and use the most detailed numerical data available to facilitate analyses of included studies. We intend to obtain these data from individuals or organisations in preference to less precise methods such as extracting numeric data from graphs. If this is necessary, two review authors will independently extract the data and a third review author will arbitrate, in case of disagreement.

Assessment of risk of bias in included studies

We will use the latest version of the Cochrane 'Risk of bias' tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risk of bias and assign judgements of this for included studies ([Higgins 2017](#)).

Measures of treatment effect

We will report dichotomous data as risk ratios with 95% confidence intervals (CI) and continuous data as mean differences (where studies used the same scale) or standardised mean differences (where studies used different scales) with 95% CI.

We will report HRQoL outcomes as mean differences for continuous data or risk ratios for dichotomous data, depending on how they are reported.

Unit of analysis issues

We will assess whether studies included one or two eyes from each participant and whether or not randomisation was conducted at the level of the participant or the eye.

Dealing with missing data

We will minimise missing outcome data by contacting individuals and organisations to obtain them. If the data are unavailable, but the level of missing data in each group and reasons for missing data in each group are similar, we will analyse available-case data if an intention-to-treat (ITT) analysis has not been performed. If authors have conducted their own ITT analysis despite missing data, we will document whether they provided any justification for the method they used to deal with missing data, and whether they compared their ITT result with an available-case result.

Assessment of heterogeneity

We will assess heterogeneity between trials by careful examination of the study reports, assessing forest plots, and examining the I^2 statistic with its 95% CI. We will consider I^2 values greater than 50% as indicative of substantial heterogeneity, suggestive that meta-analysis might not be wise; however, we will consider the consistency of the effect estimates. If all estimates are in the same direction, we might meta-analyse, even where heterogeneity is evident and comment on the heterogeneity.

Assessment of reporting biases

We will use a funnel plot to assess the risk of publication bias if there are more than 10 trials in our review.

Data synthesis

We will undertake a meta-analysis where data appears clinically, methodologically, and statistically homogeneous. We will check that participants, interventions, comparators, and outcomes are sufficiently similar to give a clinically meaningful result and that our I^2 result indicates little inconsistency (i.e. I^2 less than 50%). We will use a random-effects model unless there are fewer than three eligible studies, in which case we will use a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We do not plan to conduct subgroup analysis in future updates of the review.

Sensitivity analysis

We planned to assess the impact of including studies at high risk of bias for an outcome in one or more key domains.

'Summary of findings' table

We planned to prepare tables to summarise the findings of the review, including the assessment of the quality of evidence for all primary and secondary outcomes using the GRADE approach ([GRADEpro 2015](#)).

We planned to report subconjunctival draining minimally-invasive devices compared to the following comparison groups described under [Types of interventions](#):

- in combination with phacoemulsification compared with phacoemulsification alone;
- laser treatment;
- other MIGS techniques;
- conventional glaucoma surgery (trabeculectomy); or
- medical therapy.

We planned to report the following outcomes at medium-term follow-up (18 to 36 months) in the 'Summary of findings' table:

- Mean change in IOP measured with Goldman applanation tonometry.
- Proportion of participants who were drop-free (not using eye drops).
- Mean change in number of IOP-lowering drops taken per day.
- Proportion of participants who required further glaucoma surgery, including laser, as recorded by the investigators of the included trials.
- Mean change in health-related quality of life (HRQoL).
- Proportion of participants experiencing intraoperative complications.

- Proportion of participants experiencing postoperative complications (any time point).

RESULTS

Description of studies

Results of the search

The electronic searches yielded 539 references ([Figure 1](#)). After removal of 107 duplicates, the Cochrane Information Specialist screened the remaining 432 records and removed 308 references that were clearly irrelevant. We screened the remaining 124 references and identified one ongoing study that met the inclusion criteria ([NCT01881425](#)).

Figure 1. Study flow diagram.

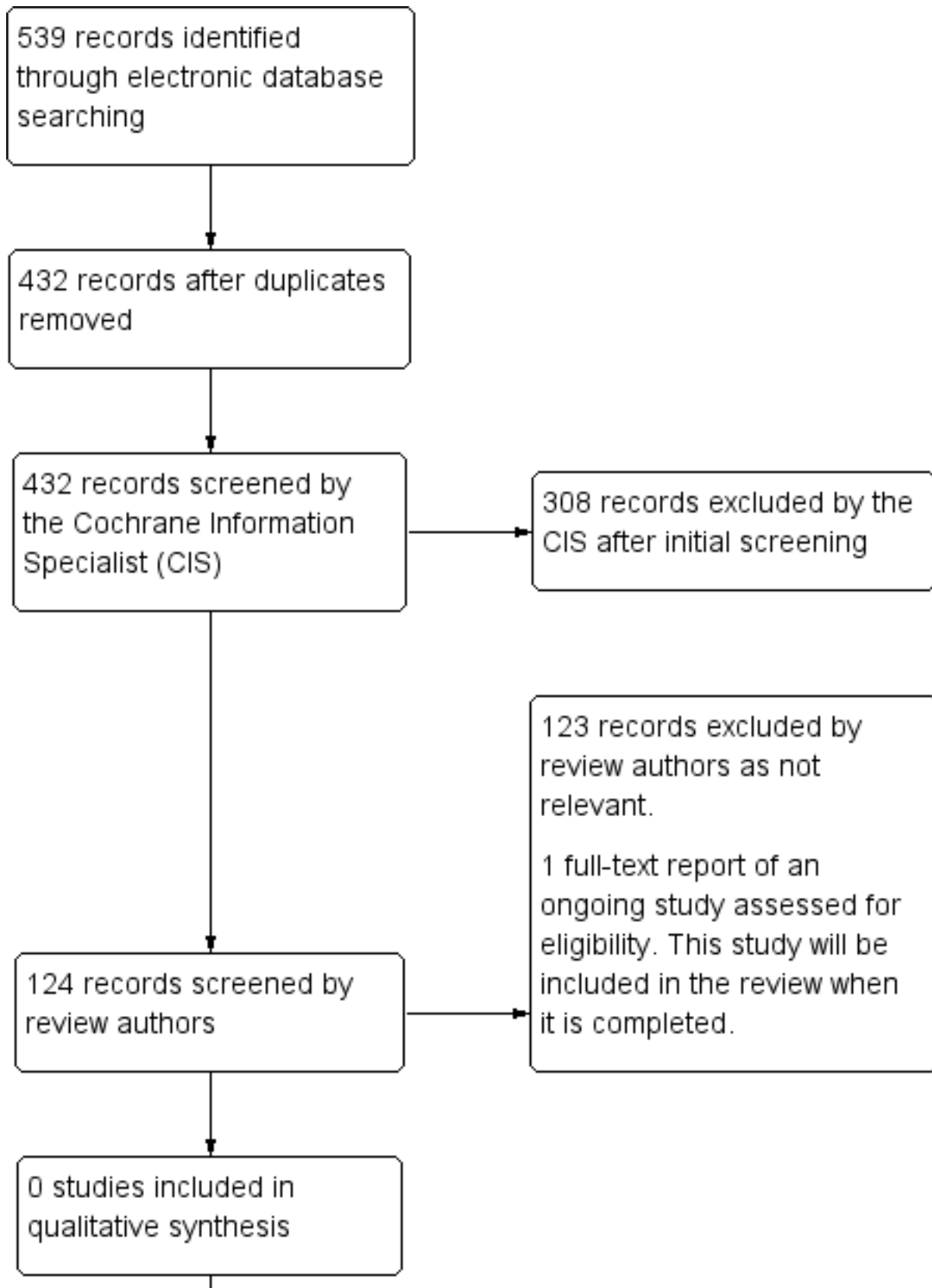
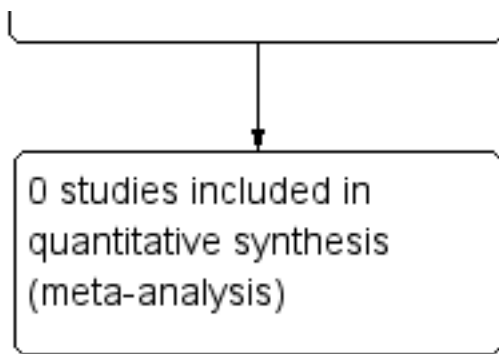


Figure 1. (Continued)



Ongoing studies

The ongoing study should be completed in November 2019. See [Ongoing studies](#) for further details.

Risk of bias in included studies

We included no published RCTs that met our inclusion criteria.

Effects of interventions

There were no completed RCTs reporting outcomes of subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma.

DISCUSSION

We found no RCTs reporting the outcomes of subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma.

We found one ongoing RCT for the InnFocus MicroShunt. We will report the outcomes of this trial when they become available should it meet our inclusion criteria.

Summary of main results

There are currently no RCTs reporting the outcomes of subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma.

Overall completeness and applicability of evidence

We performed a thorough search of available evidence as outlined in the published protocol ([King 2017](#)).

Quality of the evidence

We found no trials for inclusion in this review.

Potential biases in the review process

While we performed a thorough search of the literature, it is possible that we missed relevant published or ongoing RCTs.

Agreements and disagreements with other studies or reviews

We found no reviews for comparison.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no high-quality evidence available for the efficacy or safety of subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma. Practitioners need to take this into consideration when reviewing the treatment options for open angle glaucoma.

Implications for research

The Xen subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma has been available and used in the National Health Service for several years. Properly designed randomised controlled trials (RCTs) are needed to assess the medium- and long-term efficacy and safety of subconjunctival draining minimally-invasive glaucoma devices compared to conventional medical, laser, and surgical treatments for open angle glaucoma. The RCTs should report clinical outcomes, outcomes that are relevant to patients such as quality of life and outcomes important to service planning such as cost effectiveness.

ACKNOWLEDGEMENTS

Cochrane Eyes and Vision (CEV) will created and executed the electronic search strategies. We thank Nitin Anand and Jennifer Evans for their comments on the published protocol that forms the template for this one ([Hu 2016](#)) and on the review itself.

We thank the members of the MIGS Consortium for their input in this review.

REFERENCES

References to ongoing studies

NCT01881425 *{published data only}*

NCT01881425. InnFocus MicroShunt versus trabeculectomy study (IMS) [A randomized study comparing the safety and efficacy of the InnFocus MicroShunt glaucoma drainage system to standard trabeculectomy in subjects with primary open angle glaucoma]. clinicaltrials.gov/ct2/show/NCT01881425 (first received 17 June 2013).

Additional references

AGIS 2000

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.

Battle 2016

Battle JF, Fantes F, Riss I, Pinchuk L, Albuquerque R, Kato YP, et al. Three-year follow-up of a novel aqueous humor MicroShunt. *Journal of Glaucoma* 2016;**25**(2):e58-65.

Burr 2007

Burr JM, Mowatt G, Hernandez R, Siddiqui MA, Cook J, Lourenco T, et al. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technology Assessment* 2007;**11**(41):1-190.

CNTG Study Group 1998

Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *American Journal of Ophthalmology* 1998;**126**(4):487-97.

Covidence [Computer program]

Veritas Health Innovation. Covidence. Melbourne, Australia: Veritas Health Innovation, accessed 12 July 2018.

Francis 2011

Francis BA, Singh K, Lin SC, Hodapp E, Jampel HD, Samples JR, et al. Novel glaucoma procedures: a report by the American Academy of Ophthalmology. *Ophthalmology* 2011;**118**(7):1466-80.

Friedman 2009

Friedman DS, Okeke CO, Jampel HD, Ying GS, Plyler RJ, Jiang Y, et al. Risk factors for poor adherence to eyedrops in electronically monitored patients with glaucoma. *Ophthalmology* 2009;**116**(6):1097-105.

Gedde 2012

Gedde SJ, Herndon LW, Brandt JD, Budenz DL, Feuer WJ, Schiffman JC, et al. Postoperative complications in the tube versus trabeculectomy (TVT) study during five years of follow-up. *American Journal of Ophthalmology* 2012;**153**(5):804-14.

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006;**94**(2):130-6.

GRADEpro 2015 [Computer program]

GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed prior to 25 April 2017. Hamilton (ON): GRADE Working Group, McMaster University, 2015.

Heijl 2002

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

Higgins 2017

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), *Cochrane Handbook for Systematic Reviews of Interventions* version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Hu 2016

Hu K, Gazzard G, Bunce C, Wormald R. Ab interno trabecular bypass surgery with Trabectome for open angle glaucoma. *Cochrane Database of Systematic Reviews* 2016, Issue 8. [DOI: [10.1002/14651858.CD011693.pub2](https://doi.org/10.1002/14651858.CD011693.pub2)]

Ismail 2015

Ismail R, Azuara-Blanco A, Ramsay CR. Outcome measures in glaucoma: a systematic review of Cochrane reviews and protocols. *Journal of Glaucoma* 2015;**24**(7):533-8.

Ismail 2016

Ismail R, Azuara-Blanco A, Ramsay CR. Consensus on outcome measures for glaucoma effectiveness trials: results from a delphi and nominal group technique approaches. *Journal of Glaucoma* 2016;**25**(6):539-46.

James Lind Alliance 2013

James Lind Alliance Sight Loss, Vision Priority Setting Partnership. Setting priorities for eye research. www.sightlosspsp.org.uk (accessed 5 June 2017).

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 2013

King A, Azuara-Blanco A, Tuulonen A. Glaucoma. *BMJ* 2013;**346**:f3518.

Kirwan 2013

Kirwan JF, Lockwood AJ, Shah P, Macleod A, Broadway DC, King AJ, et al. Trabeculectomy in the 21st century: a multicenter analysis. *Ophthalmology* 2013;**120**(12):2532-9.

Le 2017

Le JT, Bicket AK, Li T. Ab interno trabecular bypass surgery with iStent for open angle glaucoma. *Cochrane Database of Systematic Reviews* 2017, Issue 8. [DOI: [10.1002/14651858.CD012743](https://doi.org/10.1002/14651858.CD012743)]

Lewis 2014

Lewis RA. Ab interno approach to the subconjunctival space using a collagen glaucoma stent. *Journal of Cataract and Refractive Surgery* 2014;**40**(8):1301-6.

Lichter 2001

Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001;**108**(11):1943-53.

Mansberger 2012

Mansberger SL, Gordon MO, Jampel H, Bhorade A, Brandt JD, Wilson B, et al. Reduction in intraocular pressure after cataract extraction: the Ocular Hypertension Treatment Study. *Ophthalmology* 2012;**119**(9):1826-31.

Okeke 2009

Okeke CO, Quigley HA, Jampel HD, Ying GS, Plyler RJ, Jiang Y, et al. Adherence with topical glaucoma medication monitored electronically the Travatan Dosing Aid study. *Ophthalmology* 2009;**116**(2):191-9.

Otarola 2017

Otarola F, Hu K, Gazzard G, Bunce C. Ab interno trabecular bypass surgery with Schlemm's Canal Microstent (Hydrus) for open angle glaucoma. *Cochrane Database of Systematic Reviews* 2017, Issue 8. [DOI: [10.1002/14651858.CD012740](https://doi.org/10.1002/14651858.CD012740)]

Peters 2013

Peters D, Bengtsson B, Heijl A. Lifetime risk of blindness in open-angle glaucoma. *American Journal of Ophthalmology* 2013;**156**(4):724-30.

Pinchuk 2008

Pinchuk L, Wilson GJ, Barry JJ, Schoepfoerster RT, Parel JM, Kennedy JP. Medical applications of poly(styrene-block-isobutylene-block-styrene) ("SIBS"). *Biomaterials* 2008;**29**(4):448-60.

Pinchuk 2015

Pinchuk L, Riss I, Batlle JF, Kato YP, Martin JB, Arrieta E, et al. The development of a micro-shunt made from poly(styrene-block-isobutylene-block-styrene) to treat glaucoma. *Journal of Biomedical Materials Research. Part B, Applied Biomaterials* 2015;**105**(1):211-21.

Quigley 2006

Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Ophthalmology* 2006;**90**(3):262-7.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Richter 2016

Richter GM, Coleman AL. Minimally invasive glaucoma surgery: current status and future prospects. *Clinical Ophthalmology* 2016;**10**:189-206.

Riss 2015

Riss I, Batlle J, Pinchuk L, Kato YP, Weber BA, Parel JM. One-year results on the safety and efficacy of the InnFocus MicroShunt depending on placement and concentration of mitomycin C. *Journal Francais d'Ophtalmologie* 2015;**38**(9):855-60.

Rodriguez-Una 2016

Rodriguez-Una I, King AJ. Postoperative follow-up regimes after glaucoma surgery in the United Kingdom. 12th European Glaucoma Society Congress; 2016 June 19-22; Prague, Czech Republic. 2016.

Sandhu 2017

Sandhu A, Jayaram H, Hu K, Bunce C, Gazzard G. Ab interno supraciliary microstent surgery for open angle glaucoma. *Cochrane Database of Systematic Reviews* 2017, Issue 9. [DOI: [10.1002/14651858.CD012802](https://doi.org/10.1002/14651858.CD012802)]

Sheybani 2015a

Sheybani A, Reitsamer H, Ahmed II. Fluid dynamics of a novel micro-fistula implant for the surgical treatment of glaucoma. *Investigative Ophthalmology and Visual Science* 2015;**56**(8):4789-95.

Sheybani 2015b

Sheybani A, Lenzofer M, Hohensinn M, Reitsamer H, Ahmed II. Phacoemulsification combined with a new ab interno gel stent to treat open-angle glaucoma: pilot study. *Journal of Cataract and Refractive Surgery* 2015;**41**(9):1905-9.

Sheybani 2016

Sheybani A, Dick HB, Ahmed II. Early clinical results of a novel ab interno gel stent for the surgical treatment of open-angle glaucoma. *Journal of Glaucoma* 2016;**25**(7):e691-6.

Tóth 2017

Tóth M, Hu K, Bunce C, Gazzard G. Endoscopic cyclophotocoagulation (ECP) for open angle glaucoma and primary angle closure. *Cochrane Database of Systematic Reviews* 2017, Issue 8. [DOI: [10.1002/14651858.CD012741](https://doi.org/10.1002/14651858.CD012741)]

References to other published versions of this review

King 2017

King AJ, Hu K, Nikita E, Mulvaney CA, Azuara-Blanco A, Stead R. Subconjunctival draining minimally-invasive

glaucoma devices for medically uncontrolled glaucoma. *Cochrane Database of Systematic Reviews* 2017, Issue 8. [DOI: [10.1002/14651858.CD012742](https://doi.org/10.1002/14651858.CD012742)]

CHARACTERISTICS OF STUDIES

Characteristics of ongoing studies [ordered by study ID]

NCT01881425

Trial name or title	A Randomized Study Comparing the Safety and Efficacy of the InnFocus MicroShunt™ Glaucoma Drainage System to Standard Trabeculectomy in Subjects with Primary Open Angle Glaucoma
Methods	Prospective, randomised, controlled, multicentre study
Participants	<p>Inclusion criteria:</p> <p>Primary open angle glaucoma on maximum tolerated glaucoma medications giving IOP of 15-40 mmHg</p> <p>Age: 40-85 years</p> <p>Exclusion criteria:</p> <p>Previous conjunctival incisional ophthalmic surgery</p> <p>Anticipated need for additional ocular surgery during the study</p> <p>Secondary glaucoma</p> <p>Any condition that prevents the device implantation or trabeculectomy in the superior region of the study eye</p>
Interventions	<p>Intervention: InnFocus MicroShunt</p> <p>Comparator: trabeculectomy</p> <p>889 enrolled but intervention and comparator numbers not specified</p>
Outcomes	<p>Primary outcome:</p> <p>> 20% decrease in diurnal IOP to 12 months' follow-up</p> <p>Secondary outcome:</p> <p>Reduction in diurnal IOP from baseline to 12 months' postoperative examination.</p> <p>Clinical follow-up will be scheduled over the course of the 24-month study, and examinations will be repeated to monitor eye health. At 1- and 2-year follow-up, diurnal IOP taken in the morning, mid-day, and afternoon in the same day will be performed. Annual follow-up will occur up to 2 years.</p>
Starting date	June 2013
Contact information	Haydee Frost, CCRC. Tel: 305-378-2651 ext 246; e-mail: hfrost@innfocusinc.com
Notes	Funding source: InnFocus Inc.

IOP: intraocular pressure

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor: [Glaucoma, Open-Angle] explode all trees
- #2 MeSH descriptor: [Intraocular Pressure] explode all trees
- #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 chronic near/2 glaucoma*
- #8 secondary near/2 glaucoma*
- #9 low near/2 tension near/2 glaucoma*
- #10 low near/2 pressure near/2 glaucoma*
- #11 normal near/2 tension near/2 glaucoma*
- #12 normal near/2 pressure near/2 glaucoma*
- #13 pigment near/2 glaucoma*
- #14 MeSH descriptor: [Exfoliation Syndrome] this term only
- #15 exfoliat* near/2 syndrome*
- #16 exfoliat* near/2 glaucoma*
- #17 pseudoexfoliat* near/2 syndrome*
- #18 pseudoexfoliat* near/2 glaucoma*
- #19 #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
- #20 Xen*
- #21 gel* near/3 (stent* or implant*)
- #22 AqueSys
- #23 InnFocus or MicroShunt*
- #24 poly styrene-block-isobutylene-block-styrene
- #25 #20 or #21 or #22 or #23 or #24
- #26 #19 and #25

Appendix 2. MEDLINE Ovid search strategy

1. randomised controlled trial.pt.
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma open angle/
14. exp intraocular pressure/
15. ocular hypertension/
16. (OAG or POAG or IOP or OHT).tw.
17. (simple\$ adj3 glaucoma\$).tw.
18. (open adj2 angle adj2 glaucoma\$).tw.
19. (primary adj2 glaucoma\$).tw.
20. (chronic adj2 glaucoma\$).tw.
21. (secondary adj2 glaucoma\$).tw.
22. (low adj2 tension adj2 glaucoma\$).tw.
23. (low adj2 pressure adj2 glaucoma\$).tw.
24. (normal adj2 tension adj2 glaucoma\$).tw.
25. (normal adj2 pressure adj2 glaucoma\$).tw.
26. (pigment\$ adj2 glaucoma\$).tw.
27. exfoliation syndrome/
28. (exfoliat\$ adj2 syndrome\$).tw.
29. (exfoliat\$ adj2 glaucoma\$).tw.

30. (pseudoexfoliat\$ adj2 syndrome\$).tw.
31. (pseudoexfoliat\$ adj2 glaucoma\$).tw.
32. or/13-31
33. Xen\$.tw.
34. (gel\$ adj3 (stent\$ or implant\$)).tw.
35. AqueSys.tw.
36. (InnFocus or MicroShunt\$).tw.
37. poly styrene-block-isobutylene-block-styrene.tw.
38. or/33-37
39. 32 and 38
40. 12 and 39

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by [Glanville 2006](#).

Appendix 3. Embase Ovid search strategy

1. exp randomised controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. open angle glaucoma/
34. intraocular pressure/
35. intraocular hypertension/
36. (OAG or POAG or IOP or OHT).tw.
37. (open adj2 angle adj2 glaucoma\$).tw.
38. (primary adj2 glaucoma\$).tw.
39. (chronic adj2 glaucoma\$).tw.
40. (secondary adj2 glaucoma\$).tw.
41. (low adj2 tension adj2 glaucoma\$).tw.
42. (low adj2 pressure adj2 glaucoma\$).tw.
43. (normal adj2 tension adj2 glaucoma\$).tw.
44. (normal adj2 pressure adj2 glaucoma\$).tw.
45. (pigment\$ adj2 glaucoma\$).tw.
46. exfoliation syndrome/

47. (exfoliat\$ adj2 syndrome\$).tw.
48. (exfoliat\$ adj2 glaucoma\$).tw.
49. (pseudoexfoliat\$ adj2 syndrome\$).tw.
50. (pseudoexfoliat\$ adj2 glaucoma\$).tw.
51. or/33-50
52. Xen\$.tw.
53. (gel\$ adj3 (stent\$ or implant\$)).tw.
54. AqueSys.tw.
55. (InnFocus or MicroShunt\$).tw.
56. poly styrene-block-isobutylene-block-styrene.tw.
57. or/52-56
58. 51 and 57
59. 32 and 58

Appendix 4. ISRCTN search strategy

" Xen OR gelatin implant OR gelatin implant OR AqueSys OR InnFocus OR MicroShunt "

Appendix 5. ClinicalTrials.gov search strategy

Xen OR gelatin implant OR gelatin implant OR AqueSys OR InnFocus OR MicroShunt

Appendix 6. WHO ICTRP search strategy

Xen OR gelatin implant OR gelatin implant OR AqueSys OR InnFocus OR MicroShunt

Appendix 7. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	Parallel group RCT <i>i.e. people randomised to treatment</i> Within-person RCT <i>i.e. eyes randomised to treatment</i> Cluster RCT <i>i.e. communities randomised to treatment</i> Cross-over RCT Other, specify	Number of study arms Method of randomisation Exclusions after randomisation Losses to follow-up Number randomised/analysed
Eyes	One eye included in study , <i>specify how eye selected</i>	Method of masking
Unit of randomisation/ unit of analysis	Two eyes included in study, both eyes received same treatment , <i>briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture of one eye and two eyes</i> Two eyes included in study, eyes received different treatments , <i>specify if correct pair-matched analysis done</i>	How were missing data handled? <i>e.g. available-case analysis, imputation methods</i> Reported power calculation (Y/N), <i>if yes, sample size and power</i> Unusual study design/issues
Participants		
Country	—	Setting
Total number of participants	<i>This information should be collected for total study population recruited into the study. If these data are reported for the people who were followed up only, please indicate.</i>	Ethnic group
Number (%) of men and women		Method of recruitment
		Participation rate

(Continued)

Mean age and age range		Equivalence of baseline characteristics (Y/N)
Inclusion criteria	—	Diagnostic criteria
Exclusion criteria	—	
Interventions		
Intervention (n =)	Number of people randomised to this group	Xen/InnFocus Implant surgical parameters, e.g. location of implant under the conjunctive or in the anterior chamber, dose of mitomycin-C used
Comparator (n =)	Intervention name	
See MECIR 65 and 70	Comparator name	Comparator parameters, e.g. dosage of drugs
	Specify whether phacoemulsification, or other intervention, performed at same time as intervention	
Outcomes		
Primary and secondary outcomes as defined in study reports	IOP at baseline IOP at follow-up Number of glaucoma medications at baseline	Planned/actual length of follow-up
See MECIR R70	Number of glaucoma medications at follow-up Intraoperative complications Postoperative complications Secondary surgery Duration of follow-up Loss to follow-up Intervals at which outcomes assessed Adverse events reported (Y/N)	
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: (if applicable)
Sources of funding	—	Date of publication
Declaration of interest	—	Reported subgroup analyses (Y/N) Were trial investigators contacted?
See MECIR 69		

CONTRIBUTIONS OF AUTHORS

Protocol

AK and EN wrote the protocol.
 All authors reviewed and approved the protocol.

Review

AS, EN, and RS screened the search results.

RS extracted the data for the ongoing study and AS checked data.
AS and AK wrote the review.
AAZ, CAM, EN, KH and RS commented on the draft.

DECLARATIONS OF INTEREST

Anthony J King undertook an invited lecture for Allergan on trabeculectomy surgery and role of phasing in glaucoma.
Anupa Shah: none known.
Eleni Nikita: none known.
Kuang Hu performs this and other forms of minimally-invasive glaucoma surgery. He lectured on "Constructing clinical trials for MIGS - the lack of evidence and what to do about it" at the Moorfields International Glaucoma Symposium 2016, sponsored by Laboratoires Thea, which is contributing an educational grant to Moorfields Eye Hospital.
Caroline A Mulvaney: none known.
Richard Stead: none known.
Augusto Azuara-Blanco has done unpaid consultancy work for Bayer (2015 and 2016) as a member of an independent panel judging the quality of care of NHS Departments of Ophthalmology. Bayer provided funds to Queen's University Belfast.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.
 - * Richard Wormald, Co-ordinating Editor for Cochrane Eyes and Vision (CEV) acknowledges financial support for his CEV research sessions from the Department of Health through the award made by the NIHR to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology.
 - * This review was supported by the NIHR, via Cochrane Infrastructure funding to the CEV UK editorial base.

The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service, or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The follow-up times for the outcomes were decided after the protocol was published.
- An additional co-author, A Shah joined the review team.
- The protocol included combination therapy with phacoemulsification as a separate comparison and also for subgroup analysis. After discussion within the review team and MIGS Consortium, we opted to include it as a separate comparison as this is likely to be a different indication.

INDEX TERMS

Medical Subject Headings (MeSH)

*Glaucoma Drainage Implants [adverse effects]; Glaucoma [*therapy]; Intraocular Pressure; Trabeculectomy

MeSH check words

Humans