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## Ab interno trabecular bypass surgery with Trabectome for open angle glaucoma (Review)

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## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
BACKGROUND . . . . .	2
OBJECTIVES . . . . .	3
METHODS . . . . .	3
RESULTS . . . . .	6
Figure 1. . . . .	7
DISCUSSION . . . . .	8
AUTHORS' CONCLUSIONS . . . . .	8
ACKNOWLEDGEMENTS . . . . .	9
REFERENCES . . . . .	9
CHARACTERISTICS OF STUDIES . . . . .	10
DATA AND ANALYSES . . . . .	13
APPENDICES . . . . .	13
CONTRIBUTIONS OF AUTHORS . . . . .	17
DECLARATIONS OF INTEREST . . . . .	17
SOURCES OF SUPPORT . . . . .	18
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . . .	18

[Intervention Review]

# Ab interno trabecular bypass surgery with Trabectome for open angle glaucoma

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## ABSTRACT

### Background

Glaucoma is the leading cause of irreversible blindness. Minimally invasive surgical techniques, such as ab interno trabecular bypass surgery, have been introduced to prevent glaucoma progressing.

### Objectives

The main objective was to assess the results at two years of ab interno trabecular bypass surgery with Trabectome for open angle glaucoma in comparison to conventional medical, laser, or surgical treatment in terms of efficacy and safety. A secondary objective was to examine the effects of Trabectome surgery in people who have concomitant phacoemulsification in comparison to those who do not have concomitant phacoemulsification.

### Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 4), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to May 2016), EMBASE (January 1980 to May 2016), the ISRCTN registry ([www.isrctn.com/editAdvancedSearch](http://www.isrctn.com/editAdvancedSearch)), ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) ([www.who.int/ictrp/search/en](http://www.who.int/ictrp/search/en)). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 12 May 2016.

### Selection criteria

We included only randomised controlled trials (RCTs) of ab interno trabecular bypass surgery with Trabectome.

### Data collection and analysis

We planned to have two review authors independently extract data from reports of included studies using a data collection form.

## Main results

One randomised controlled trial identified from ClinicalTrials.gov, NCT00901108, met the criteria for inclusion. This study has subsequently been terminated. The ClinicalTrials.gov record indicates that the investigators plan to complete 12 months of follow-up and analysis on 19 participants already recruited into the trial.

## Authors' conclusions

There is currently no high-quality evidence for the outcomes of ab interno trabecular bypass surgery with Trabectome for open angle glaucoma. Properly designed RCTs are needed to assess the long-term efficacy and safety of this technique.

## PLAIN LANGUAGE SUMMARY

### Minimally invasive surgery with Trabectome for glaucoma

#### What was the aim of this review?

The aim of this Cochrane Review was to learn if a Trabectome improves the surgical treatment of glaucoma. Cochrane researchers collected and analysed all relevant studies to answer this question and found no completed studies.

#### Key messages

There are no data comparing Trabectome 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. The Trabectome is a device that could help make this surgery less invasive, which may be safer than standard surgery.

#### What are the main results of the review?

The review authors did not find any completed studies.

#### How up-to-date is this review?

The review authors searched for studies published up to 12 May 2016.

## BACKGROUND

### 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. Open angle glaucoma (OAG) is the most common type, accounting for three-quarters of cases (Quigley 2006). In one large population cohort, 1 in 6 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) over the long term (AGIS 2000; CNTG Study Group 1998; Heijl 2002; Kass 2002). Approaches to reducing intraocular pressure (IOP) include medical therapy, laser treatments, and surgery. As 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 patients developing perioperative complications (Kirwan 2013; Lichter 2001), and 7% to 18% of cases requiring re-operation (Gedde 2012; Kirwan 2013). These techniques are therefore often reserved for disease that is progress-

ing despite other treatments (King 2013).

### Description of the intervention

A number of minimally invasive surgical techniques have recently been developed with the aim of achieving long-term reduction of IOP with a better safety profile than conventional surgery (Francis 2011). Among them, ab interno trabecular bypass surgery (also known as trabeculotomy ab interno and trabeculectomy ab interno) with the Trabectome (NeoMedix, Tustin, California) is a Food and Drug Administration (FDA) approved and CE marked treatment.

### How the intervention might work

The trabecular meshwork is the eye's main site of resistance to outflow of aqueous humour (Overby 2009). The Trabectome is designed to selectively ablate a portion of the trabecular meshwork, enabling aqueous humour to have direct access to the canal of Schlemm and thence the collector channels (Francis 2006). This is intended to promote aqueous outflow, thereby reducing IOP. Tissue ablation is performed electrosurgically using a 19.5-gauge instrument, which is introduced into the eye via a 1.6-mm incision in the cornea.

### Why it is important to do this review

Consultation with patients and healthcare professionals has identified a need for better treatments for glaucoma (James Lind Alliance 2013). Minimally invasive glaucoma procedures carry the possibility of safe and effective long-term reduction of IOP, removing concerns about permanent vision loss due to non-adherence to eye drops. A single treatment may also be more acceptable to patients than daily and indefinite self administration of eye drops. Initial results of ab interno trabecular bypass surgery with the Trabectome were reported in 2005 (Minckler 2005). Post-market surveillance data show that more than 4600 treatments were performed between 2004 and 2013 at over 200 centres worldwide (Mosaed 2014; NeoMedix, on file). In light of the potential benefits for patients and the widespread uptake of the technique, it is important to critically evaluate the evidence for whether treatment with the Trabectome is both efficacious and safe. Importantly, Trabectome surgery may be combined with phacoemulsification (cataract surgery), a sight-restoring operation to remove the natural lens of the eye when it has lost clarity. Since phacoemulsification itself reduces IOP (Mansberger 2012), we planned specifically to examine the evidence for efficacy of Trabectome treatment in people who have concomitant phacoemulsification in comparison to those who do not have concomitant phacoemulsification.

## OBJECTIVES

The main objective was to assess the results at two years of ab interno trabecular bypass surgery with Trabectome for OAG in comparison to conventional medical, laser, or surgical treatment in terms of efficacy and safety. A secondary objective was to examine the effects of Trabectome surgery in people who have concomitant phacoemulsification in comparison to those who do not have concomitant phacoemulsification.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included randomised controlled trials (RCTs) only. We included all study reports published in the English language (or which have been translated into English), irrespective of their publication status. We planned to exclude within-person studies because of the potential for medical treatments, such as topical beta blockers, used for one eye to influence the outcome in the other eye (Piltz 2000).

#### Types of participants

Participants could have 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 (provided these were clearly stated). Participants with ocular hypertension, normal tension glaucoma, or possible glaucoma (suspects for glaucoma) were also included. We applied no restrictions regarding location, setting, or demographic factors.

#### Types of interventions

The intervention was ab interno trabeculotomy performed with the Trabectome (NeoMedix, Tustin, California). Although it is possible to ablate a variable amount of the trabecular meshwork (typically an arc of 40 degrees), and to vary the electrosurgical power employed (Francis 2006), we did not apply any particular inclusion or exclusion criteria around these or other treatment delivery parameters. The comparators were conventional glaucoma treatment, whether using medical therapy, laser treatment, or conventional glaucoma surgery. Since phacoemulsification cataract surgery is known to reduce IOP (Mansberger 2012), we planned to examine the effect of the intervention in people who had phacoemulsification at the same time compared to people who did not have phacoemulsification at the same time.

## Types of outcome measures

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

## Primary outcomes

The primary outcome was the proportion of participants who were drop-free (not using eye drops) at two years after randomisation. Several different glaucoma outcome measures have been specified as primary outcomes in other Cochrane Reviews and Protocols (Ismail 2015). A recent 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). We chose a patient-centred primary outcome.

## Secondary outcomes

Secondary outcomes were:

1. Mean change in IOP, measured using Goldmann applanation tonometry, from randomisation to two years.
2. The proportion of participants experiencing intra- and postoperative complications from randomisation to two-year follow-up including but not restricted to the following:
  - i) 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);
  - ii) bleeding, as recorded by the investigators;
  - iii) endophthalmitis, as recorded by the investigators;
  - iv) 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);
  - v) secondary surgery, as recorded by the investigators.
3. Change to any health-related quality of life measures, from randomisation to two-year follow-up, reported as differences in means or odds ratios for continuous and binary data, respectively.

## Search methods for identification of studies

### Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 4), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946

to May 2016), EMBASE (January 1980 to May 2016), the ISRCTN registry ([www.isrctn.com/editAdvancedSearch](http://www.isrctn.com/editAdvancedSearch)), ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) ([www.who.int/ictrp/search/en](http://www.who.int/ictrp/search/en)). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 12 May 2016.

See Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), ISRCTN (Appendix 4), ClinicalTrials.gov (Appendix 5), and the ICTRP (Appendix 6).

## Searching other resources

We planned to search the reference lists of included studies for other possible studies and to contact any individuals or organisations whom we believed may have conducted or be conducting relevant RCTs. We also searched the website of the manufacturer (NeoMedix Inc., Tustin, California; [www.trabectome.com](http://www.trabectome.com)) for any information on forthcoming trials.

## Data collection and analysis

### Selection of studies

Two review authors independently screened titles and abstracts of all articles identified by the search. Where abstracts were not available, we planned to screen full-text articles. Two review authors would independently assess full-text reports of all potentially eligible studies. In case of disagreement regarding eligibility, a third review author would arbitrate. If we rejected any full-text reports, we would record the reasons for this.

### Data extraction and management

We planned to extract data from reports of included studies using a data collection form, which was to be developed and piloted on the first five studies included. Two review authors would independently extract study characteristics from reports of each study and enter the data into RevMan (RevMan 2014). In case of disagreement, a third independent review author would arbitrate. We planned to collect the following information on the characteristics of included studies (Appendix 7).

- Year of publication.
- Year of study.
- Country of study.
- Sample size.
- Participation rate.
- Method of recruitment.
- Eligibility criteria.
- Diagnostic criteria.

- Method of randomisation.
- Method of masking.
- Number of study arms.
- Types of participants.
- Types of interventions.
- Types of comparators.
- Use of phacoemulsification at the same time as the intervention.

We planned to collect the following data regarding outcomes (Appendix 7).

- IOP at baseline.
- IOP at follow-up.
- Number of glaucoma medications at baseline.
- Number of glaucoma medications at follow-up.
- Intraoperative complications.
- Postoperative complications or secondary surgery.
- Duration of follow-up.
- Loss to follow-up.
- Intervals at which outcomes were assessed.

Where data on included studies were missing or unclear, we planned to contact the individuals or organisations involved to obtain clarification. We intended to collect and use the most detailed numerical data available to facilitate analyses of included studies. We would attempt to obtain this data from individuals or organisations in preference to less precise methods such as extracting numeric data from graphs. If this was necessary, two review authors would independently extract the data, and a third review author would arbitrate in case of disagreement.

### Assessment of risk of bias in included studies

We planned to 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 2011).

### Measures of treatment effect

The primary outcome was the proportion of participants drop-free at two years after randomisation. We planned to use an odds ratio as the treatment effect measure. In assessing this effect measure, we planned to report how the prescribing of IOP-lowering eye drops was determined during follow-up. We planned to examine whether the people measuring IOP and those deciding upon the prescribing of IOP-lowering eye drops were masked to the treatment group. We planned to report mean change in IOP from randomisation to two years after randomisation. We would report secondary safety outcomes as odds ratios. We would report health-related quality of life outcomes as differences in means or odds ratios for continuous and binary data, respectively.

### Unit of analysis issues

We planned to assess whether included studies have included one or two eyes from each participant and whether or not randomisation had been conducted at the level of the participant or the eye. There is a potential for medical treatments, such as topical beta blockers, used for one eye to influence the outcome in the other eye (Piltz 2000). We therefore planned to exclude studies that adopted a paired design. Surgery to lower IOP in one eye may also affect the IOP of the fellow eye (Radcliffe 2010).

### Dealing with missing data

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

### Assessment of heterogeneity

We planned to assess heterogeneity between trials by careful examination of the study reports, assessing forest plots, and an examination of the  $I^2$  value with its confidence interval. We would consider  $I^2$  values greater than 50% as indicative of substantial heterogeneity and, therefore, suggestive that meta-analysis might not be wise; however, we would give consideration to the consistency of the effect estimates. If all estimates were in the same direction, we might meta-analyse even where heterogeneity was evident and comment on the heterogeneity.

### Assessment of reporting biases

We planned to use a funnel plot to assess the risk of publication bias if we included more than 10 trials in the review.

### Data synthesis

We planned to undertake a meta-analysis where data appeared clinically, methodologically, and statistically homogeneous. We would check that participants, interventions, comparators, and outcomes were sufficiently similar to give a clinically meaningful result and that our  $I^2$  result indicated little inconsistency (that is  $I^2$  less than 50%). If all estimates were in the same direction, we might meta-analyse even where heterogeneity was evident but would comment on this. We planned to use a random-effects model unless there were fewer than three eligible studies, in which case we would use a fixed-effect model.

### **Subgroup analysis and investigation of heterogeneity**

We planned to undertake a subgroup analysis. The effect modifier to be examined was the use of phacoemulsification as a co-intervention. Phacoemulsification has been shown to reduce IOP ([Mansberger 2012](#)). We would therefore analyse whether the effect of Trabectome surgery differed depending on whether phacoemulsification had been used as a co-intervention.

### **Sensitivity analysis**

We planned to assess the impact of including studies at high risk of bias.

### **Summary of findings**

We planned to prepare tables to summarise the findings of the review, including the assessment of the quality of evidence for all outcomes using the GRADE approach ([Langendam 2013](#)).

We were to report all outcomes considered in the review in the summary.

## **RESULTS**

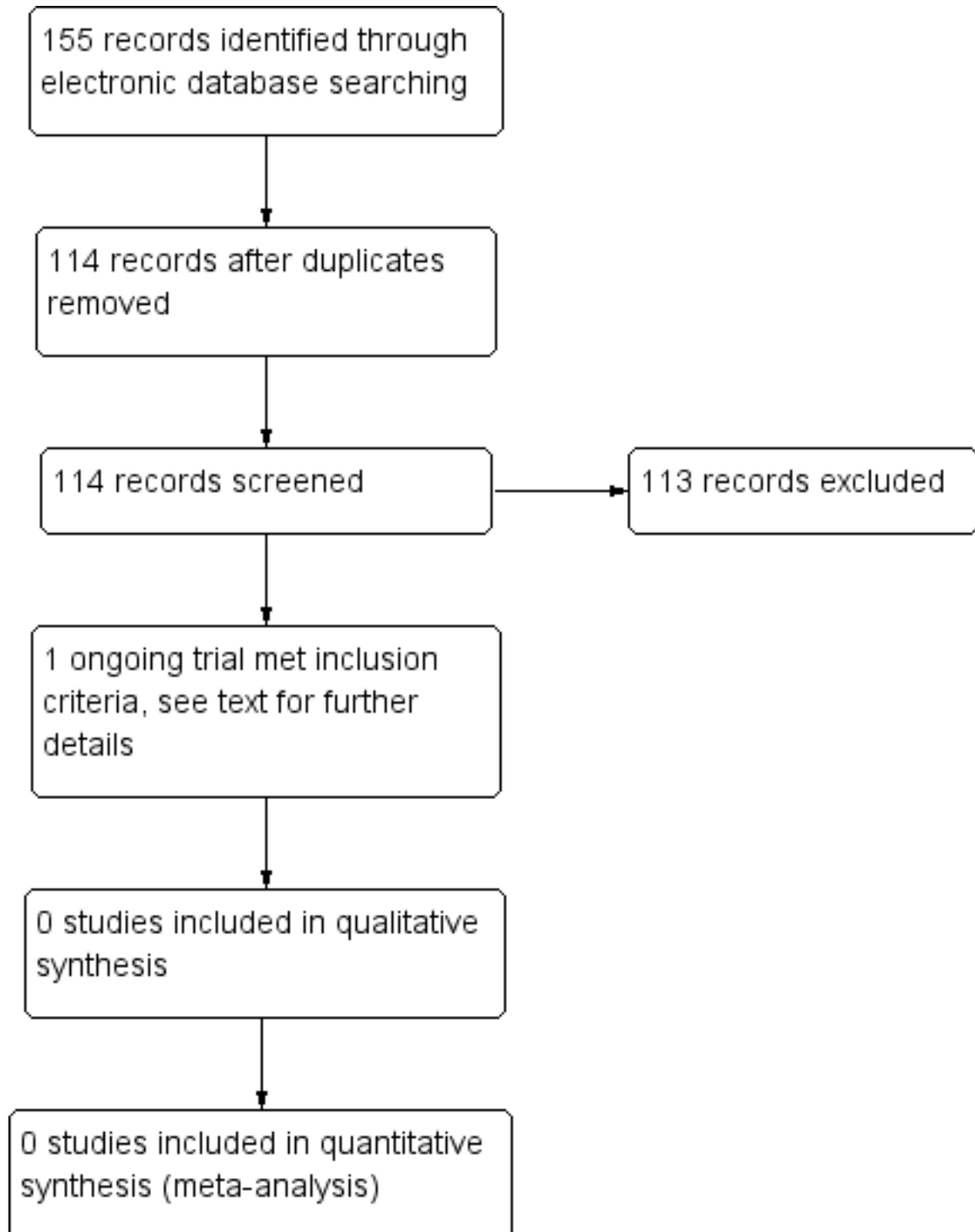
### **Description of studies**

#### **Results of the search**

The electronic searches yielded a total of 155 references ([Figure 1](#)). The Cochrane Information Specialist removed 41 duplicate records, and two review authors (GG and KH) independently screened the remaining 114 reports for potentially eligible studies, namely possible RCTs.



Figure 1. Study flow diagram.



There was no disagreement between the authors regarding eligibility of any of the search results. We assessed no full-text reports, however we identified one ongoing trial as potentially relevant (see [Characteristics of ongoing studies](#)).

We are not aware of any other individuals or organisations who have conducted or may be conducting relevant RCTs. A search of the website of the manufacturer (NeoMedix Inc., Tustin, California; [www.trabectome.com](http://www.trabectome.com)) did not yield any information on forthcoming trials.

### Included studies

We did not find any published RCTs that met the inclusion criteria.

### Excluded studies

We did not exclude any trials after obtaining the full-text report.

### Ongoing studies

One RCT, [NCT00901108](#), met the criteria for inclusion. However, at the time of the original search for this review, it was an ongoing study recruiting participants and had not yet been published. This trial compares combined Trabectome and cataract extraction with intraocular lens implantation against combined trabeculectomy with mitomycin C and cataract extraction with intraocular lens insertion. We note that the listing on ClinicalTrials.gov has subsequently been updated (8 June 2015) to indicate that enrolment to the study was closed early owing to “lack of clinical equipoise essential for patient randomisation/recruitment”. The investigators planned to complete 12 months of follow-up and analysis on participants already recruited into the trial. On 23 February 2016 the ClinicalTrials.gov record was updated noting that: “A total of 19 participants were recruited with follow up to one year. Study analysis is pending.” For further information on this study, see the [Characteristics of ongoing studies](#) table.

### Risk of bias in included studies

We have included no trials in this review for reasons previously mentioned.

### Effects of interventions

There were no completed RCTs reporting the outcomes of ab interno trabeculotomy performed with the Trabectome for open angle glaucoma.

There are currently no RCTs reporting the outcomes of ab interno trabecular bypass surgery with Trabectome for open angle glaucoma.

One RCT is in progress. Enrolment to this trial was closed early, which will reduce its power to detect differences in safety and efficacy. The trial will report outcomes up to 12 months of follow-up, but not more long-term outcomes.

### Summary of main results

There are currently no RCTs providing evidence for the outcomes of ab interno trabecular bypass surgery with Trabectome for open angle glaucoma.

### Overall completeness and applicability of evidence

We believe that our conclusions are supported by a thorough search of available evidence, as outlined in the published protocol ([Hu 2015](#)).

### Quality of the evidence

We did not identify any trials for inclusion in this review.

### Potential biases in the review process

The review authors may not be aware of individuals or organisations who have conducted or may be conducting relevant RCTs, therefore it is possible that relevant RCTs have not been identified.

### Agreements and disagreements with other studies or reviews

A review examining IOP and glaucoma medications following ab interno trabecular bypass surgery with Trabectome was published recently ([Kaplowitz 2016](#)). This review included only prospective or retrospective case series or cohorts, so the results are not comparable with our review.

## DISCUSSION

## AUTHORS' CONCLUSIONS

## Implications for practice

There is currently no high-quality evidence for the outcomes of ab interno trabecular bypass surgery with Trabectome for open angle glaucoma. Practitioners need to take this into account when considering treatment options for open angle glaucoma.

## Implications for research

Ab interno trabecular bypass surgery with Trabectome has been used for over 10 years. Properly designed RCTs are needed to assess the long-term efficacy and safety of this technique compared to conventional glaucoma treatments for people with open angle glaucoma. These RCTs should assess outcomes that are relevant

to patients, such as freedom from using eye drops. If superiority is demonstrated compared to conventional treatments, the next step would be to determine whether Trabectome is superior to other forms of minimally invasive glaucoma surgery.

## ACKNOWLEDGEMENTS

We thank Iris Gordon of Cochrane Eyes and Vision for creating and executing the electronic search strategies. We thank Nitin Anand and Jennifer Evans for their comments on the protocol/review and Anupa Shah for assisting with the review process. We thank Claire Allcock for proofreading the final version.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of ongoing studies [ordered by study ID]

NCT00901108

Trial name or title	Trabectome versus trabeculectomy with mitomycin C in patients with open angle glaucoma
Methods	Single-centre, single-surgeon, parallel-group randomised controlled trial with 2 study arms 1 eye included in study (method of selection not specified) Originally intended to recruit 52 participants (26 participants per study arm). However, recruitment was closed early (total recruitment = 19) owing to “clearer indications for each technique over time leading to lack of clinical equipoise essential for patient randomization/recruitment”
Participants	Characteristics of participants are unknown. Total number of participants recruited is 19 Inclusion criteria: <ol style="list-style-type: none"> <li>1. Age 40 to 85 years</li> <li>2. Open angle glaucoma (including pseudo exfoliative glaucoma)</li> <li>3. Open angles (<math>\geq</math> Shaffer grade II)</li> <li>4. Inadequately controlled IOP requiring surgical intervention</li> <li>5. Visually significant cataract</li> <li>6. Willing to complete quality of life questionnaires</li> <li>7. Capable of informed consent and available for at least 1 year follow-up</li> </ol> Exclusion criteria: <ol style="list-style-type: none"> <li>1. Any form of angle-closure glaucoma</li> <li>2. Secondary open angle glaucomas</li> <li>3. Absence of clear angle landmarks on gonioscopy</li> <li>4. Other ocular disease that may affect assessments of visual acuity, visual field, or accurate tonometry</li> <li>5. Previous angle surgery or filtering procedure</li> <li>6. Steroid use within the preceding 3 months</li> <li>7. Presence of significant comorbidities</li> </ol>
Interventions	Trabectome-IOL: Combined Trabectome and cataract extraction with intraocular lens insertion (n = unknown) Trab-IOL: Combined trabeculectomy with mitomycin C and cataract extraction with intraocular lens insertion (n = unknown)
Outcomes	Primary outcome measures: <ul style="list-style-type: none"> <li>• Mean IOP at 6 months</li> <li>• Surgical complication rates (Time Frame: intraoperative and postoperative up to 12 months)</li> </ul> Secondary outcome measures: <ul style="list-style-type: none"> <li>• Mean difference in IOP from baseline to 6 months</li> <li>• Mean IOP at 12 months</li> <li>• Quality of life measures (Time Frame: preoperative and postoperative at 6 and 12 months)</li> <li>• Mean number of glaucoma medications (Time Frame: 12 months)</li> <li>• Visual acuity (Time Frame: 12 months)</li> <li>• Need for additional laser (excluding suture lysis) and surgical interventions (Time Frame: 12 months)</li> </ul>
Starting date	November 2009

**NCT00901108** (Continued)

Contact information	Principal Investigator Karim F Damji University of Alberta
Notes	

IOP: intraocular pressure

## DATA AND ANALYSES

This review has no analyses.

## 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\*
- #18p 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 trabectome
- #21 ab interno trabeculectomy or trabeculectomy ab interno
- #22 ab interno trabeculotomy or trabeculotomy ab interno
- #23 trabecular near/2 bypass\*
- #24 #20 or #21 or #22 or #23
- #25 #19 and #24

### Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.
2. (randomized 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. trabectome.tw.
34. (Ab interno adj2 (trabeculectomy or trabeculotomy)).tw.
35. (trabecular adj2 bypass\$).tw.
36. or/33-35
37. 32 and 36
38. 12 and 37

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

### **Appendix 3. EMBASE (OvidSP) search strategy**

1. exp randomized 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. trabectome.tw.
53. (ab interno adj2 (trabeculectomy or trabeculotomy)).tw.
54. (trabecular adj2 bypass\$).tw.
55. or/52-54
56. 51 and 55
57. 32 and 56

#### **Appendix 4. ISRCTN search strategy**

trabectome OR trabecular bypass OR ab interno trabeculectomy OR ab interno trabeculotomy

#### **Appendix 5. ClinicalTrials.gov search strategy**

(trabectome OR trabecular bypass OR ab interno trabeculectomy OR ab interno trabeculotomy)

## Appendix 6. ICTRP search strategy

trabectome OR trabecular bypass OR ab interno trabeculectomy OR ab interno trabeculotomy = Intervention

## Appendix 7. Data on study characteristics

Mandatory items		Optional items
<b>Methods</b>		
Study design	<ul style="list-style-type: none"> <li>· <b>Parallel-group RCT</b> <i>i.e. people randomised to treatment</i></li> <li>· <b>Within-person RCT</b> <i>i.e. eyes randomised to treatment</i></li> <li>· <b>Cluster RCT</b> <i>i.e. communities randomised to treatment</i></li> <li>· <b>Cross-over RCT</b></li> <li>· Other, specify</li> </ul>	Number of study arms Method of randomisation Exclusions after randomisation Losses to follow-up Number randomised/analysed Method of masking 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
Eyes Unit of randomisation/unit of analysis	<ul style="list-style-type: none"> <li>· <b>1 eye included in study, specify how eye selected</b></li> <li>· <b>2 eyes included in study, both eyes received same treatment, 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 1 eye and 2 eyes</b></li> <li>· <b>2 eyes included in study, eyes received different treatments, specify if correct pair-matched analysis done</b></li> </ul>	
<b>Participants</b>		
Country	-	Setting Ethnic group
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>	Method of recruitment Participation rate
Number (%) of men and women		Equivalence of baseline characteristics (Y/N)
Average age and age range		Diagnostic criteria
Inclusion criteria		-
Exclusion criteria	-	
<b>Interventions</b>		
Intervention (n = ) Comparator (n = )	<ul style="list-style-type: none"> <li>· Number of people randomised to this group</li> <li>· Intervention name</li> </ul>	Trabectome surgical parameters, <i>e.g. degrees of meshwork ablated, electrosurgical power</i> Comparator parameters, <i>e.g. dosage of drugs</i>

(Continued)

	<ul style="list-style-type: none"> <li>· Comparator name</li> <li>· Specify whether phacoemulsification or other intervention performed at same time as intervention</li> </ul>	
<b>Outcomes</b>		
Primary and secondary outcomes <i>as defined in study reports</i>	<ul style="list-style-type: none"> <li>· IOP at baseline</li> <li>· IOP at follow-up</li> <li>· Number of glaucoma medications at baseline</li> <li>· Number of glaucoma medications at follow-up</li> <li>· Intraoperative complications</li> <li>· Postoperative complications or secondary surgery</li> <li>· Duration of follow-up</li> <li>· Loss to follow-up</li> <li>· Intervals at which outcomes assessed</li> <li>Adverse events reported (Y/N)</li> </ul>	Planned/actual length of follow-up
<b>Notes</b>		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: <i>(if applicable)</i> Date of publication
Sources of funding	-	Reported subgroup analyses (Y/N) Were trial investigators contacted?
Declaration of interest	-	

## CONTRIBUTIONS OF AUTHORS

Kuang Hu and Catey Bunce wrote the protocol. Kuang Hu, Catey Bunce, Gus Gazzard, and Richard Wormald reviewed and approved the protocol.

Gus Gazzard and Kuang Hu screened the search results. Kuang Hu wrote the review. Kuang Hu, Catey Bunce, Gus Gazzard, and Richard Wormald reviewed and approved the review.

## DECLARATIONS OF INTEREST

The review authors are seeking funding to address the subject of this review.

Kuang Hu performs Trabectome surgery. He has 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.

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The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

### External sources

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The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences between the protocol and review.