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

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

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[Intervention Protocol]

Subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma

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ABSTRACT

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

The main objective is to evaluate the efficacy and safety of subconjunctival draining minimally-invasive glaucoma devices in treating people with OAG and ocular hypertension whose condition is inadequately controlled with drops.

BACKGROUND

This protocol is based on the protocol from the published review on ab interno trabecular bypass surgery with Trabectome for open angle glaucoma (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. Open angle glaucoma (OAG) is the commonest type, accounting for three-quarters of cases (Quigley 2006). In one large population cohort, one in six patients 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. 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 patients developing perioperative complications (Kirwan 2013; Lichter 2001) and reoperation being needed in 7% to 18% (Gedde 2012; Kirwan 2013). Therefore, they are often reserved for disease that is progressing despite other treatments (King 2013).

Description of the intervention

Recently, a number of minimally-invasive surgical techniques (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 former has been approved in Europe for the treatment of glaucoma and is CE marked treatment, but does not have 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 Infocus 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 intraocular pressure (IOP). Both devices are routinely augmented with mitomycin C, an antimetabolite which is injected subconjunctivally at the time of surgery to reduce postoperative scaring 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 implant in both Europe and the USA (Batlle 2016; Rodriguez-Una 2016; Sheybani 2015b).

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 when used 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 implants is responsible for additional IOP reduction.

This Cochrane Review will be 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, California) (Hu 2016), Hydrus Schlemm´s canal Microstent (Ivantis Inc., Irvine, California) (Otarola 2017), endoscopic cytophotocoagulation (ECP) (Endo Optiks, Waltham, Massachusetts) (Tóth 2017) and iStent and iStent inject (Glaukos Corporation, Laguna Hills, CA, USA).

OBJECTIVES

The main objective is to evaluate the efficacy and safety of subconjunctival draining minimally-invasive glaucoma devices in treating people with OAG and ocular hypertension whose condition is inadequately controlled with drops.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) only. We will include reports of RCTs prepared in any language, irrespective of their publication status.

Types of participants

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

Types of interventions

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

The Xen Gelatin 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 (Batlle 2016; Pinchuk 2015; Riss 2015) is approximately 70 microns in diameter, with an outer diameter of 350 microns and a length of approximately 8.5 mm. 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 will compare subconjunctival draining minimally-invasive glaucoma devices to:

1. laser treatment (selective laser trabeculoplasty or argon laser trabeculoplasty);
2. other MIGS techniques;
3. conventional glaucoma surgery (trabeculectomy)
4. medical therapy; or
5. in combination with phacoemulsification compared with phacoemulsification alone (since phacoemulsification cataract surgery is known to reduce IOP (Mansberger 2012)).

Types of outcome measures

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

Primary outcomes

The primary outcome will be mean change in IOP measured up to two years following baseline, with Goldman applanation tonometry.

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 participant-centred primary outcome.

Secondary outcomes

Secondary outcomes will be:

1. Proportion of participants who are drop-free (not using eye drops) at two years follow-up.
2. Mean change in number of IOP-lowering drops taken per day from baseline to two years follow-up.
3. Proportion of participants who achieve an IOP $\leq$ 21 mmHg at one year.
4. Proportion of participants who achieve an IOP $\leq$ 17 mmHg at one year.
5. Proportion of participants who achieve an IOP $\leq$ 14 mmHg at one year.
6. Proportion of participants experiencing intra- and postoperative complications from randomisation to two-year follow-up 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).
    - Secondary surgery, as recorded by the investigators.
7. Mean change in health-related quality of life (QoL) at two years.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomised controlled trials and controlled clinical trials. There will be no language or publication year restrictions.

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

Searching other resources

We will search the reference lists of included studies for other possible studies and will contact any individuals or organisations whom we believe may have conducted or be conducting relevant

RCTs. We will also search the website of the manufacturers (AqueSys Inc., Aliso Viejo, CA, USA; InnFocus Inc, Miami, FL, USA), for any information on forthcoming trials.

Data collection and analysis

Selection of studies

Two review authors working independently will screen titles and abstracts of all articles identified by the search, using web-based online review management software (Covidence 2015). If abstracts are not available, we will screen full-text articles. Full-text copies of all reports retained after this initial screening will be sought, and will be assessed independently by two review authors for inclusion in the review.. If there is disagreement regarding eligibility, a third review author will arbitrate. If any full-text reports are rejected, we will record the reasons for this.

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 studies included. Two review authors will work independently to extract study characteristics from reports of each study and enter the data into Review Manager 5 (RevMan 5) (Review Manager 5 2014). If there is disagreement, a third independent review author will arbitrate.
We will 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 will 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 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 will attempt 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 independent review authors will 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* (Higgins 2011) to assess the risk of bias and assign judgements of this for included studies.

Measures of treatment effect

We will report dichotomous data as risk ratios with 95% confidence intervals (CI) and continuous data as mean differences or standardised mean differences with 95% CI.
Health-related quality of life outcomes will be reported as mean differences for continuous data or risk ratios for dichotomous data, depending on how it is reported.

Unit of analysis issues

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

Dealing with missing data

We will endeavour to minimize 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 may simply 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 have provided any justification for the method they have used to deal with missing data, and whether they have compared their ITT result with an available case result.

Assessment of heterogeneity

We will assess the 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 will consider I^2 values greater than 50% as indicative of substantial heterogeneity, suggestive that meta analysis might not be wise - however, consideration will be given to the consistency of the effect estimates. If all estimates are in the same direction, we might meta-analyse, even where heterogeneity is evident; we will 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 within our review.

Data synthesis

We will undertake a meta-analysis where data appear 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%). If all estimates are in the same direction, we might meta-analyse, even where heterogeneity is evident but will comment on this. 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

Phacoemulsification has been shown to reduce IOP (Mansberger 2012). We will undertake a subgroup analysis to examine the effects of Xen or InnFocus devices, with or without phacoemulsification.

Sensitivity analysis

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

Summary of findings

We will prepare tables to summarise the findings of the review, including the assessment of the quality of evidence for all outcomes using the GRADE approach (GRADEpro 2014). All outcomes considered in the review will be reported in the summary.
We will report the following outcomes in the 'Summary of findings' table and the comparison groups described under Types of interventions: subconjunctival draining minimally-invasive devices compared with laser treatment, other MIGS techniques, conventional glaucoma surgery (trabeculectomy), medical therapy or in combination with phacoemulsification compared with phacoemulsification alone.

1. Proportion of participants who are drop-free (not using eye drops) at two years follow-up.
2. Mean change in number of IOP-lowering drops taken per day from baseline to two years follow-up.
3. Mean change in IOP, measured using Goldmann applanation tonometry, from baseline to two years follow-up.
4. Health-related quality of life at two years follow-up.
5. Intraoperative complications.
6. Postoperative complications, up to two years follow-up.
7. Secondary glaucoma surgery, including laser, as recorded by the investigators of the included trials between baseline and two years follow-up.

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

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* *Indicates the major publication for the study*

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. 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$).tw.
32. or/13-31
33. Xen$.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 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$).tw.
51. or/33-50
52. Xen$.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. 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.e. people randomised to treatment* · **Within-person RCT** *i.e. eyes randomised to treatment* · **Cluster RCT** *i.e. communities randomised to treatment* · **Cross-over RCT** · Other, specify	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? *e.g. available case analysis, imputation methods* Reported power calculation (Y/N*), if yes, sample size and power* Unusual study design/issues

(*Continued*)

Eyes Unit of randomisation/ unit of analysis	· **One eye included in study**, *specify how eye selected* · **Two 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 one eye and two eyes* · **Two eyes included in study, eyes received different treatments,** *specify if correct pair-matched analysis done*	
Participants		
Country		Setting Ethnic group Method of recruitment
Total number of participants	*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.*	
Number (%) of men and women		Number (%) of men and women
Average age and age range		Average age and age range
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n=) Comparator (n=) ***See MECIR 65 and 70***	· Number of people randomised to this group · Intervention name · Comparator name · Specify whether phacoemulsification, or other intervention, performed at same time as intervention	Xen/Innfocus Implant surgical parameters, e.g. location of implant under the conjunctive or in the anterior chamber, dose of mitomycic-C used, Comparator parameters, *e.g. dosage of drugs*
Outcomes		
Primary and secondary outcomes *as defined in study reports* ***See MECIR R70***	· 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	Planned/actual length of follow-up

(*Continued*)

	· 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)* Date of publication Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding		
Declaration of interest ***See MECIR 69***		

CONTRIBUTIONS OF AUTHORS

Anthony King and Eleni Nikita wrote the protocol. All authors reviewed and approved the protocol**.**

DECLARATIONS OF INTEREST

Anthony J King has undertaken invited lecture for Allergan on trabeculectomy surgery and role of phasing in glaucoma.

Kuang Hu performs this and other forms of minimally-invasive glaucoma 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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Caroline A Mulvaney: None known

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