NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of microinvasive subconjunctival insertion of a trans-scleral gelatin stent for primary open-angle glaucoma

Primary open-angle glaucoma is a progressive condition that causes long-term increase of pressure within the eye. This damages the nerve that connects the eye to the brain (optic nerve) and may gradually lead to permanent loss of sight.

This procedure involves placing a tiny soft gel tube into the eye to create a new channel to allow excess fluid to drain out. The aim is to reduce pressure in the eye.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in June 2017.

Procedure name

- Microinvasive subconjunctival insertion of a trans-scleral gelatin stent for primary open-angle glaucoma

Specialist societies

- Royal College of Ophthalmologists.

Description

Indications and current treatment

Open-angle glaucoma is a chronic condition associated with increased intraocular pressure, which leads to progressive damage to the optic nerve. Early stages are usually asymptomatic but as the condition progresses it causes visual impairment and, if untreated, blindness.

Treatment is usually eye drops containing drugs that either reduce the production of aqueous humor or increase its drainage. Surgical procedures such as trabeculectomy, inserting drainage tubes, deep sclerectomy, viscocanalostomy or laser trabeculoplasty may also be used.

What the procedure involves

Microinvasive insertion of a trans-scleral gelatin stent via the ab interno (anterior chamber) approach for treating open-angle glaucoma is a minimally invasive procedure. It involves implanting a gelatin stent, a collagen-derived drainage device, to reduce intraocular pressure. The procedure creates an artificial bypass channel and drainage pathway from the anterior chamber into the non-dissected tissue of the subconjunctival space to improve drainage and outflow of aqueous humor.

This procedure can be done at the same time as phacoemulsification and intraocular lens insertion for treating cataracts.

Under local or topical anaesthesia, a small incision is made in the cornea, and the anterior chamber is filled with viscoelastic. A preloaded implant injector is then advanced through the same corneal incision and directed towards the scleral spur. The injector needle is directed through the sclera to emerge under the conjunctiva, approximately 2 mm to 3 mm behind the limbus. The soft and permanent gelatin stent is then injected, to traverse the anterior chamber, sclera and conjunctival space. After placement is checked (using a gonioscopy mirror) the viscoelastic is exchanged for a balanced salt solution and the injector is withdrawn. The corneal incision is usually self-sealing but is sometimes sutured. Subconjunctival injection of mitomycin-C may be done during the procedure.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to microinvasive subconjunctival insertion of a trans-scleral gelatin stent for primary open-angle glaucoma. The following databases were searched, covering the

period from their start to 12 January 2017: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with primary open-angle glaucoma.
Intervention/test	Microinvasive subconjunctival insertion of a trans-scleral gelatin stent.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 84 patients from 2 case series[1, 2] and 2 case reports[3, 4].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on microinvasive subconjunctival insertion of a trans-scleral gelatin stent for primary open-angle glaucoma

Study 1 Sheybani A [2016]

Details

Study type	**Case series (prospective)**
Country	Canada, USA, Germany, Australia, Venezuela, Poland and Mexico (multicentre)
Recruitment period	Not reported
Study population and number	**n=49 patients (49 eyes) with open-angle glaucoma (OAG)** glaucoma type: primary OAG n=38, exfoliation n=6, juvenile n=3, pigmentary n=2 failed previous glaucoma procedures: trabeculectomy with mitomycin-C n=21, tube shunt n=2, argon or selective laser trabeculoplasty n=9; trans-scleral cyclophotocoagulation n=3 medicated intraocular pressure (IOP, mmHg): mean 23.1±4.1; preoperative medications: mean 3±1.1
Age and sex	Mean 64.3 years; 41 (20/49) male
Patient selection criteria	Included: Patients with a diagnosis of OAG (including exfoliating and pigmentary glaucoma), juvenile OAG, and at least 2 clock hours of mobile conjunctiva in the quadrant of planned device placement and if 2 consecutive IOP readings were more than 18 mmHg and less than 35 mmHg with or without medication. Patients with previous glaucoma, cataract surgery or laser treatment. Excluded: Patients with angle closure, congenital, neovascular or other secondary glaucoma; a history of uveitis or endophthalmitis, or previous corneal surgery or intraocular surgery other than cataract or glaucoma surgery or aphakia.
Technique	Subconjunctival filtration surgery combined with cataract surgery (phacoemulsification) Implantation of a gelatin stent (first generation Xen 140) that shunts aqueous flow from the anterior chamber to the subconjunctival space was performed through an ab interno approach at the time of cataract surgery (after routine clear corneal phacoemulsification with intraocular lens implantation) without adjuvant mitomycin-C (MMC). 8 different surgeons were involved and the same surgeon performed the surgery at each centre. Glaucoma medications were added over the postoperative period as needed. Postoperative needling with MMC was performed if the IOP was above target and determined by the physician.
Follow-up	**12 months**
Conflict of interest/source of funding	The primary author was the principal investigator for this study sponsored by the manufacturer (Aquesys). Two authors were clinical investigators and 1 author was a paid consultant to the company.

Analysis

Follow-up issues: short follow-up, 4 patients were excluded from the analysis because 1 was lost to follow-up and 3 were excluded by the study criteria.

Study design issues: prospective case series in 8 university and private practice centres, study was not designed to address safety. IOP was measured by Goldman applanation tonometry (2 measurements in each eye). Complete success was defined as a postoperative intraocular pressure (IOP) of less than 18 mmHg and more than a 20% reduction at 12 months without glaucoma medication. Partial success was defined as an IOP of less than 18 mmHg with a more than 20% reduction at 12 months with or without glaucoma medication. Failure was defined as loss of light perception vision or worse, a need for additional glaucoma surgery or less than a 20% reduction in the IOP from baseline at 12 months.

Study population issues: 27 patients had previous incisional glaucoma surgery, 17 patients (eyes) were pseudophakic before device implantation. 33% patients were not white.

Other issues: there may be some overlap of patients with study 2.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **45 patients (45 eyes)**

IOP and medications use

Preoperative IOP mm Hg (mean±SD)	**Postoperative IOP mmHg (mean±SD)**	**P value**
23.1±4.1	14.7±3.7	<0.0001
Preoperative medication classes (mean±SD)	**Postoperative medication classes (mean±SD)**	**P value**
3.0	1.3	<0.0001

At 12 months, 42% (19/45) patients were off medication completely, 16% (8/45) patients were on the same number of medications, 8% (4/45) patients were on 1 additional medication.

Partial success rate at 12 months 89% (40/45)

Complete success rate off medication 40% (18/45)

Kaplan-Meier curve with failure criteria applied depicts procedure survival over 1 year.

Visual acuity

Preoperative CDVA	**Postoperative CDVA**	**P value**
20/30	20/28	0.424

Needling rate: 47% (21/45) required needling and of those 3 were needled with mitomycin-C.

Safety

Adverse events

	% (n)
Corneal oedema (trace)	1
Shallow anterior chambers (needing injection in the first postoperative week with ophthalmic viscosurgical device, restored to normal depth)	9 (4/45)

Over 12 months, no endophthalmitis, wound leak, device exposure or migration, macular oedema, choroidal effusion or haemorrhage, iritis, or retinal detachment occurred.

Abbreviations used: CDVA, corrected distance visual acuity; IOP, intraocular pressure; SD, standard deviation.

Study 2 Sheybani A [2015]

Details

Study type	**Case series (prospective)**
Country	Canada, Austria, USA (multicentre)
Recruitment period	Not reported
Study population and number	**n=37 patients (37 eyes) with open-angle glaucoma (OAG)** glaucoma type: primary OAG n=23, exfoliation n=9, pigmentary n=1 previous glaucoma procedures: argon or selective laser trabeculoplasty n=11; trans-scleral cyclophotocoagulation n=3 medicated intraocular pressure (IOP, mmHg): mean 22.4±4.2; preoperative medications: mean 2.5±1.4
Age and sex	Mean 69.6 years; 38 (14/37) male
Patient selection criteria	Included: Patients with a diagnosis of OAG (including exfoliating and pigmentary glaucoma), a visually significant cataract, uncontrolled IOP despite maximum tolerated medical therapy, and at least 2 clock hours of mobile conjunctiva in the quadrant of planned device placement and if 2 consecutive IOP readings were more than 18 mmHg and less than 35 mmHg with or without medication. Patients with previous glaucoma surgery and or laser treatment. Excluded: Patients with previous cataract surgery, a history of uveitis, or previous corneal surgery of any kind, those with glaucoma other than the types listed above.
Technique	Subconjunctival filtration surgery combined with cataract surgery (phacoemulsification) Implantation of a gelatin stent (2 models, either Xen 140 or Xen 63 with lumen width variations) that shunts aqueous flow from the anterior chamber to the subconjunctival space was performed through an ab interno approach at the time of cataract surgery (after routine clear corneal phacoemulsification with intraocular lens implantation) without adjuvant mitomycin-C (MMC). The same surgeon performed the surgery at each centre. Glaucoma medications were added over the postoperative period as needed. Postoperative needling with MMC was performed if the IOP was above target and determined by the physician.
Follow-up	**12 months**
Conflict of interest/source of funding	The primary author has received travel reimbursement from the manufacturer (Aquesys) and 1 author is a paid consultant to the company. The study was supported by Aquesys.

Analysis

Follow-up issues: 3 patients were lost to follow-up.

Study design issues: prospective case series in 7 international university and private practice centres, study was not designed to address safety. Intraocular pressure (IOP) was measured by Goldman applanation tonometry (2 measurements in each eye). Complete success was defined as a postoperative IOP of less than 18 mmHg and more than a 20% reduction at 12 months without glaucoma medications. Qualified success was defined as an IOP of less than 18 mmHg with a 20% reduction at 12 months with or without glaucoma medication. Failure was defined as loss of light perception vision or worse, a need for additional glaucoma surgery or less than a 20% reduction in the IOP from baseline at 12 months.

Study population issues: no patients had previous incisional glaucoma surgery, 2 patients could not tolerate their medications and were not on topical therapy before surgery.

Other issues: the device was not standardised (2 lumen sizes were studied) and is still being developed. Postoperative management was also not standardised because these are the results from initial experience with the implant. There might be some overlap of patients with study 1.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 37 patients (37 eyes)

IOP and medication use
<table>
<tr><th>Preoperative IOP mm Hg (mean±SD)</th><th>Postoperative IOP mmHg (mean±SD)</th><th>P value</th></tr>
<tr><td>22.4±2.4</td><td>15.4±3.0</td><td><0.0001</td></tr>
<tr><th>Preoperative medication classes (mean±SD)</th><th>Postoperative medication classes (mean±SD)</th><th>P value</th></tr>
<tr><td>2.5±1.4</td><td>0.9±1.0</td><td><0.0001</td></tr>
</table>
Qualified success rate at 12 months 85.3% (29/34)
Complete success rate off medication 47.1% (16/34)
There were no failed procedures
50% (17/34) patients were completely off medication at 12 months compared with 5% (2/34) patients preoperatively.

Visual acuity
<table>
<tr><th>Preoperative CDVA (logMAR)</th><th>Postoperative CDVA (logMAR)</th><th>P value</th></tr>
<tr><td>0.30</td><td>0.12</td><td>0.01</td></tr>
</table>
Needling rate: 32% (12/34) required needling and of those, 6 were needled with MMC and 6 were needled with 5-fluorouracil.

There were no differences in outcomes between the 2 devices.</td><td>Over 12 months, no endophthalmitis, wound leak, device exposure or migration, macular oedema, choroidal effusion or haemorrhage, iritis, or retinal detachment occurred.</td></tr>
<tr><td colspan="2">Abbreviations used: CDVA, corrected distance visual acuity; IOP, intraocular pressure; SD, standard deviation.</td></tr>
</table>

Study 3 Fea A [2015]

Details

Study type	**Case report**
Country	Italy
Recruitment period	2014-15
Study population and number	**n=1 patient** with a long-term failed prior trabeculectomy and a badly scarred superior bleb with increased IOP and severe visual field damage.
Age and sex	51 year old male
Patient selection criteria	
Technique	Minimally invasive glaucoma surgery (with Xen Aquesys subconjunctival shunt implantation) performed.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Key efficacy and safety findings

Safety
Number of patients analysed: **1** **Stent exposure** The stent was placed nasally and close to an area of scarred conjunctiva from the previous trabeculectomy (previous bleb); the IOP was well controlled but on day 15 the stent became partially exposed due to extremely thin and weak conjunctiva and the nasal location. **Treatment**: the conjunctiva over the stent exposed area was removed and the stent was patched by an amniotic membrane transplant and a conjunctival autograft. Six months after surgery the IOP is under control (lower than 14 mmHg) without medication and with complete visual recovery.
Abbreviations used: IOP, intraocular pressure.

Study 4 Fernandez-Gracia A [2015]

Details

Study type	**Case report**
Country	Spain
Recruitment period	2014-15
Study population and number	**n=1** patient with primary open-angle glaucoma in both eyes
Age and sex	69 year old; sex not reported
Patient selection criteria	
Technique	Minimally invasive glaucoma surgery (with ab interno Xen Aquesys subconjunctival shunt implantation) performed under topical anaesthesia.
Follow-up	**4 months**
Conflict of interest/source of funding	None

Key efficacy and safety findings

Safety
Number of patients analysed: **1** **Hypertrophic bleb** Patient presented with hypertrophic bleb and mechanical ectropion a few weeks after surgery. Topical medical treatment was given but the condition persisted. **Surgical treatment: bleb drainage, viscoelastic tamponade of stent and tissue adhesion** Under topical anaesthesia 'dry lake' procedure (surgical emptying of bleb) was done to drain the hypertrophic bleb following blockage of the ab interno stent with viscoelastic and bleb sealing with tissue adhesive. Immediate symptom improvement and bleb reduction were seen and IOP reduced without any medication. No complications were seen.
Abbreviations used: IOP, intraocular pressure.

Efficacy

Intraocular pressure control, with and without medication

In a multicentre case series of 49 patients (49 eyes) with open-angle glaucoma implanted with an ab interno gelatin stent without mitomycin-C, mean intraocular pressure significantly reduced from 23.1±4.1 mmHg at baseline to 14.7±3.7 mmHg at 12-month follow-up ($p<0.0001$)[1]. This was a reduction of 36% from baseline.

In another multicentre case series of 37 patients (37 eyes) with open-angle glaucoma implanted with an ab interno gelatin stent combined with phacoemulsification, mean intraocular pressure significantly reduced from 22.4±2.4 mmHg at baseline to 15.4±3.0 mmHg at 12-month follow-up ($p<0.0001$)[2].

Medication use

In the multicentre case series of 49 patients (49 eyes), the mean number of different classes of medication taken reduced significantly from 3.0 at baseline to 1.3 at 12-month follow-up ($p<0.0001$). At 12 months 42% (19/45) of patients were completely off medication, 16% (8/45) were on the same number of medications and 8% (4/45) were on 1 additional medication compared with baseline[1].

In the multicentre case series of 37 patients (37 eyes), the mean number of different classes of medication taken reduced significantly from 2.5±1.4 at baseline to 0.9±1.0 at 12-month follow-up ($p<0.0001$). At 12 months 50% (17/34) of patients were completely off medication compared with 5% (2/34) of patients preoperatively[2].

Success rate

In the multicentre case series of 49 patients (49 eyes), the partial success rate (defined as postoperative intraocular pressure less than 18 mmHg with more than a 20% reduction at 12 months with or without glaucoma medication) was 89% (40/45) and the complete success rate (defined as postoperative intraocular pressure less than 18 mmHg with more than a 20% reduction at 12 months without glaucoma medication) was 40% (18/45)[1].

In the multicentre case series of 37 patients (37 eyes), at 12 month follow-up the qualified success rate (not defined) was 85.3% (29/34) and the complete success rate (defined as postoperative intraocular pressure less than 18 mmHg with more than a 20% reduction at 12 months without glaucoma medication) was 47.1% (16/34). There were no failed procedures[2].

Visual acuity

In the multicentre case series of 37 patients (37 eyes), visual acuity improved from a preoperative corrected distance visual acuity of 0.30 logMAR to 0.12 logMAR postoperatively (p=0.01)[2]. In the multicentre case series of 49 patients (49 eyes), visual acuity was unchanged from baseline to 12-month follow-up (20/30 to 20/28, p=0.424)[1].

Safety

Stent exposure

Partial stent exposure was reported in a case report of 1 patient 15 days after stent implantation. This was close to an area of scarred conjunctiva (previous superior bleb) from a previous failed trabeculectomy. The authors report that this was because of an extremely weak and thin conjunctiva and also because of the nasal location. The conjunctiva over the exposed area was removed and replaced by an amniotic membrane and a conjunctival autograft. Six months after surgery, the stent was well-covered, intraocular pressure was well-controlled without medication and complete visual acuity regained[3].

Hypertrophic bleb

Hypertrophic bleb with mechanical ectropion a few weeks after surgery was reported in a case report of 1 patient who had subconjunctival stent implantation for primary open-angle glaucoma. Topical medical treatment was first given but the condition persisted. Surgical emptying of the bleb was done to drain it, after blockage of the ab interno stent with viscoelastic and bleb sealing with tissue adhesive. Immediate symptom improvement and bleb reduction were seen. Intraocular pressure reduced without any medication. No complications were reported[4].

Other events

Corneal oedema was reported in 1 patient at 12 months in the case series of 49 patients. Shallow anterior chambers (needing injection with a dispersive ophthalmic viscosurgical device in the first postoperative week) were reported in 9% (4/45) of patients in the same study. These returned to normal depth within 1 week after injection.

Validity and generalisability of the studies

- The Xen gel implant initially had 3 different lumen diameters. There is very little published evidence (2 small case series) on Xen 140 and Xen 63. The only device now recommended by the manufacturer is Xen 45 (with a smaller lumen) which is currently under investigation. There is no published evidence on this. The evidence on Xen 140 and Xen 63 is not directly comparable to the recommended device.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Trabecular stent bypass microsurgery for open-angle glaucoma. NICE interventional procedure guidance 575 (2017). Available from http://www.nice.org.uk/guidance/IPG575
- Trabeculotomy ab interno for open-angle glaucoma. NICE interventional procedure guidance 397 (2011). Available from http://www.nice.org.uk/guidance/IPG397
- Canaloplasty for primary open-angle glaucoma. NICE interventional procedure guidance 260 (2008). Available from http://www.nice.org.uk/guidance/IPG260

NICE guidelines

- Glaucoma: diagnosis and management. NICE guideline 85 (2009). Available from http://www.nice.org.uk/guidance/CG85. This guidance is currently under review and is expected to be updated in November 2017. For more information, see https://www.nice.org.uk/guidance/indevelopment/gid-ng10017
- Glaucoma in adults. NICE quality standard 7 (2011). Available from https://www.nice.org.uk/guidance/qs7

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One Specialist Adviser Questionnaire for microinvasive subconjunctival insertion of a

trans-scleral gelatin stent for primary open-angle glaucoma was submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team when preparing this overview.

Issues for consideration by IPAC

- Ongoing studies:
  - NCT02006693: Post-market multicentre evaluation of the XEN implant in moderate primary open-angle glaucoma, n=200, location: Europe and Venezuela, completion date March 2017.
  - NCT02036541: A prospective multicentre clinical trial designed to evaluate the safety and performance of the AqueSys XEN 45 glaucoma implant in refractory glaucoma with adjuvant mitomycin-C, n=60, location: USA, completion date September 2016.

References

1. Sheybani A, Lenzhofer M, Hohensinn M et al (2015). Phacoemulsification combined with a new ab interno gel stent to treat open-angle glaucoma: Pilot study. Journal of cataract and refractive surgery. Vol 41 (9) pp 1905-9.
2. Sheybani A, Burkhard Dick H, Ahmed IIK (2016). Early Clinical Results of a Novel Ab Interno Gel Stent for the Surgical Treatment of Open-angle Glaucoma. J Glaucoma 25(7):e691-6.
3. Fea A, Cannizzo PML, Consolandi G et al (2015). Managing Drawbacks in Unconventional Successful Glaucoma Surgery: A Case Report of Stent Exposure. Case reports in ophthalmological medicine pp 847439.
4. Fernandez-Garcia A, Romero C, and Garzon N (2015). "Dry Lake" technique for the treatment of hypertrophic bleb following XEN Gel Stent placement. Archivos de la Sociedad Espanola de Oftalmologia. Vol 90 (11) pp 536-8.

Appendix A: Additional papers on microinvasive subconjunctival insertion of a trans-scleral gelatin stent for primary open-angle glaucoma

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Manasses DT and Au Leon (2016).The New Era of Glaucoma Micro-stent Surgery. Ophthalmology and therapy (5) 2 135-146.	Review	This review summarises the current published literature on these devices, including Sclemm's canal stents (iStent, Hydrus), Suprachoroidal stents (CyPass, iStent supra), and subconjunctival stents (Xen, Innfocus).	Review on devices used for minimally invasive glaucoma surgery.
Lewis RA (2014). Ab interno approach to the subconjunctival space using a collagen glaucoma stent. Journal of cataract and refractive surgery (40) 8 1301-6.	Review of the development of a new, soft, and permanent ab interno collagen implant (XEN gel stent) to optimize aqueous drainage to the subconjunctival space.	Preclinical and human eye testing shows that the implant does not seem to occlude inside the lumen and the implant material does not appear to cause tissue reaction in the eye. The ab interno placement of the stent offers an alternative for lowering IOP with a minimally invasive procedure, minimum conjunctival tissue disruption, restricted flow to avoid hypotony, and long-term safety.	Pre-clinical testing results only.
Brandao LM and Grieshaber MC (2013). Update on Minimally Invasive Glaucoma Surgery (MIGS) and New Implants. Journal of ophthalmology 705915.	Review on minimally invasive glaucoma surgery and new devices.	The clinical results of the latest techniques and devices are presented by their approach, ab interno (trabeculotomy, excimer laser trabeculotomy, trabecular microbypass, suprachoroidal shunt, and intracanalicular scaffold) and ab externo (canaloplasty, Stegmann Canal Expander, suprachoroidal Gold microshunt). Some of these procedures produce a limited IOP reduction compared to trabeculectomy. Currently, MIGS is performed in glaucoma patients with early to moderate disease and preferably in combination with cataract surgery.	Review of various approaches and devices.
Hohberger B, Welge-Luen UC and Lammer R (2016). ICE-Syndrome: A Case Report of Implantation of a Microbypass Xen Gel Stent After DMEK Transplantation. Journal of Glaucoma no pagination.	Case report N=1 patient with secondary glaucoma due to unilateral iridocorneal endothelial syndrome after descement membrane endothelial keratoplasty operation. Xen45 gel stent glaucoma surgery	A successful implantation of Xen45 gel stent. This may be a promising option for minimally invasive glaucoma surgery in difficult situations, as low adverse effects, good post-surgery visual acuity and sufficient regulation of intraocular pressure can be seen.	Larger studies with longer follow-up included in table 2.

Nihr Hsric (2015). XEN Gel Stent for glaucoma treatment (Structured abstract). Health Technology Assessment Database 4.	Review of Xen gel stent (glaucoma drainage implant) in patients with primary open-angle glaucoma where previous treatments have failed.		Abstract only. Review
Richter GM. and Coleman AL (2016). Minimally invasive glaucoma surgery: current status and future prospects. Clinical ophthalmology (Auckland, N.Z.) (10) 189-206.	Review on current approaches for minimally invasive glaucoma surgery. Data on each surgical procedure are reviewed in this article, patient selection lessons learned to date are discussed, and expectations for the future are examined.	The current approaches include: increasing trabecular outflow (Trabectome, iStent, Hydrus stent, gonioscopy-assisted transluminal trabeculotomy, excimer laser trabeculotomy); suprachoroidal shunts (Cypass micro-stent); reducing aqueous production (endocyclophotocoagulation); and subconjunctival filtration (XEN gel stent).	No evidence on Xen gel implant.
Sheybani A, Reitsamer H and Ahmed IIK (2015). Fluid Dynamics of a Novel Micro-Fistula Implant for the Surgical Treatment of Glaucoma. Investigative ophthalmology & visual science (56) 8 4789-95.	Experimental study on Xen 45 gel stent for treatment of glaucoma.	The XEN 45 achieved a steady-state pressure calculated at 7.56 mm Hg at 2.5 muL/min. At the same flow rate, the Ex-Press device and Baerveldt tubing reached steady-state pressures of 0.09 and 0.01 mm Hg, respectively.	Experimental study on fluid dynamics.

Appendix B: Related NICE guidance for microinvasive subconjunctival insertion of a trans-scleral gelatin stent for primary open-angle glaucoma

Guidance	Recommendations
Interventional procedures	**Trabecular stent bypass microsurgery for open-angle glaucoma. NICE interventional procedure guidance 575 (2017).** 1.1 Current evidence on the safety of trabecular stent bypass microsurgery for open-angle glaucoma raises no major safety concerns. Evidence on efficacy is adequate in quality and quantity. Therefore, this procedure may be used provided that standard arrangements are in place for clinical governance, consent and audit. 1.2 Trabecular stent bypass microsurgery for open-angle glaucoma should only be done by clinicians with specific training in the procedure. **Trabeculotomy ab interno for open-angle glaucoma. NICE interventional procedure guidance 397 (2011).** 1.1 Current evidence on the safety and efficacy of trabeculotomy ab interno for open-angle glaucoma is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Patient selection should be carried out in units that specialise in glaucoma treatment that can offer a range of treatment options. 1.3 NICE encourages the collection and publication of further data on long-term efficacy. **Canaloplasty for primary open-angle glaucoma. NICE interventional procedure guidance 260 (2008).** 1.1 Current evidence on the safety and efficacy of canaloplasty for primary open-angle glaucoma is inadequate in both quality and quantity. Therefore, this procedure should only be used in the context of research or formal prospective data collection. Clinicians are encouraged to collaborate in the collection and publication of data. 1.2 Further publication of safety and efficacy outcomes will be useful. The Institute may review the procedure upon publication of further evidence.

NICE guidelines	**Glaucoma: diagnosis and management. NICE guideline 85 (2009).** This guidance is currently under review and is expected to be updated in November 2017. 1.4.6 Check the person's adherence to their treatment and eye drop instillation technique in people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss despite pharmacological treatment. If adherence and eye drop instillation technique are satisfactory offer one of the following: □ alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP □ laser trabeculoplasty □ surgery with pharmacological augmentation (MMC or 5-FU) as indicated If the pharmacological treatment option is chosen, after trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5-FU) as indicated or laser trabeculoplasty. 1.4.7 Offer surgery with pharmacological augmentation (MMC or 5-FU) as indicated to people with COAG who are at risk of progressing to sight loss despite treatment. Offer them information on the risks and benefits associated with surgery. 1.4.8 Consider offering people with COAG who are intolerant to a prescribed medication: •alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) or •a preservative-free preparation if there is evidence that the person is allergic to the preservative. After trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5‑FU) as indicated or laser trabeculoplasty. 1.4.9 After surgery offer people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss one of the following: □ pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP □ further surgery □ laser trabeculoplasty or cyclodiode laser treatment. 1.4.10 Offer people with COAG who prefer not to have surgery or who are not suitable for surgery:

	□ pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP □ laser trabeculoplasty or cyclodiode laser treatment.

Appendix C: Literature search for microinvasive subconjunctival insertion of a trans-scleral gelatin stent for primary open-angle glaucoma

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	12/01/2017	Issue 1 of 12, January 2017
HTA database (Cochrane)	12/01/2017	Issue 11 of 12, November 2016
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	12/01/2017	Issue 4 of 4, October 2016
MEDLINE (Ovid)	12/01/2017	1946 to December Week 1 2016
MEDLINE In-Process (Ovid)	12/01/2017	January 10, 2017
EMBASE (Ovid)	12/01/2017	1974 to 2017 Week 02
PubMed	12/01/2017	n/a
BLIC (British Library)	12/01/2017	n/a

Trial sources searched on 25 10 2016

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 25 10 2016

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

MEDLINE search strategy

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Glaucoma, Open-Angle/ or Glaucoma/

2 glaucom*.tw.

3 POAG.tw.

4 Ocular Hypertension/

5 Intraocular Pressure/

6 ((ocular* or intraocul* or eye*) adj4 (hypertens* or tension or pressur*)).tw.

7 IOP.tw.

8 or/1-7

9 (Glaucom* adj4 filtrat* surger*).tw.

10 Glaucoma Drainage Implants/

11 ((aqeuous or glaucom*) adj4 (stent* or micro-stent* or tube* or device* or implan* or shunt*)).tw.

12 ((collagen or gelatin* or gel*) adj4 (stent* or micro-stent* or tube* or device* or implan* or shunt*)).tw.

13 (ab-interno or "ab interno").tw.

14 ((minimal* or micro*) adj4 glaucom*).tw.

15 MIGS.tw.

16 (space* or drain* or pathway* or channel* or bypass* or by-pass*).tw.

17 or/9-16

18 (subconjunctiv* or sub-conjunctiv*).tw.

19 8 and 17 and 18

20 ((xen adj4 (stent* or implant*)) or aquesys or microshunt* or micro-shunt*).tw.

21 19 or 20

22 animals/ not humans/

23 21 not 22