South African National Essential Medicine List
Adult Hospital Medication Review Process
Component: AH Chp 18 - Eye

MEDICINE REVIEW

1. Executive Summary

Date: 31 August 2023
Medicine (INN): Mitomycin C and 5-fluorouracil (5-FU)
Medicine (ATC): L01DC03 and L01BC02
Indication (ICD10 code): H40
Patient population: Adjunctive therapy in adult patients requiring trabeculectomy surgery for glaucoma
Prevalence of condition: The overall prevalence of glaucoma in South Africa is stated at 4.5% (Baboolal SO et al, 2018), with estimates of 5 to 7% in the black population and 3 to 5% in the white population (Schellack N et al., 2017)
Level of Care: Adult Hospital Level (regional level of care)
Prescriber Level: Specialist
Motivator/reviewer name(s): G Thom , Z Adam, F Moti, L Visser, M McCaul
PTC affiliation:

Key findings

- In 2020, there were an estimated 76 million people with glaucoma worldwide. Africa has the highest incidence and prevalence of blindness compared to other regions, with glaucoma accounting for 15% of blindness.(Baboolal SO et al, 2018).
- Lowering intra-ocular pressure (IOP) is the only modifiable risk factor in the management of glaucoma. Treatment includes pharmacological management, laser therapy or surgery. Trabeculectomy is the most common type of surgery for glaucoma management for patients unresponsive to pharmacological management. Based on estimates by content expert reviewer (LV), less than 1000 trabeculectomies are conducted in the public sector locally. Adjunctive therapy with the antimetabolites mitomycin C (MMC) and 5 fluorouracil (5-FU) is reported to be effective in managing the risks of bleb failure (failure of the drainage flap created during trabeculectomy due to scarring) through a reduction in postoperative scarring.
- We conducted a review of efficacy and safety of intraoperative MMC or 5-FU for the management of adult glaucoma sufferers undergoing filtration surgery (trabeculectomy).
- We identified two systematic reviews (Wilkins M et al., 2005) (Green E et al., 2014) as relevant to our review question.

MMC:

- Patients at high risk of surgical failure who received intraoperative MMC were less likely to have failed surgery at 12 months) when compared to placebo/no intraoperative treatment, resulting in 35 fewer per 100 (from 22 to 46 fewer) surgical failures. Control 49/97 (50%) failed vs MMC 15/96 (15%) failed, ARR 35%, NNT 3 (95% CI 2 to 5) to prevent one failed surgery. (RR 0.32, 95% CI 0.20 to 0.53, 4 trials, n= 193 participants, moderate certainty of evidence).
- Patients undergoing surgery for the first time were less likely to have failed surgery at 12 months, relative to no antimetabolite or placebo, resulting in 20 fewer per 100 (from 12 to 30 fewer) with MMC. Control 30/107 (28%) vs intervention 18/231 (8%) ARR 20%, NNT 5 to prevent one failed surgery (95% CI 3 to 9), (RR 0.29, 95% CI: 0.16 to 0.53, 4 trials, n= 338 participants, moderate certainty of evidence).

- Intraoperative use of MMC reduced mean intraocular pressure (IOP). The mean pressure difference was -5.31 mmHg (95% CI: -3.85 to -6.76 mmHg) in high risk patients and -5.41 mmHg, 95% CI: -3.49 to -7.34 mmHg) in patients operated on for the first time, when compared to placebo or no antimetabolite. In clinical practice, a 1mmHg reduction in IOP can be regarded as significant.
- Overall, there was no increase in serious sight threatening side effects such as endophthalmitis with MMC. This analysis is limited by lack of power. Only one study reported on this outcome in patients receiving surgery for the first time: no cases of endophthalmitis occurred (0/229 in the MMC group compared to 0/71 in the control group.

5-FU

- Early trials with 5-FU were primarily focused on the postoperative injections which are now rarely used due to the more labour intensive follow up by clinicians and inconvenience for patients due to the series of postoperative injections. In more recent trials, 5-FU has been administered intraoperatively using sponges moistened with 25mg/mL or 50mg/mL 5-FU solution, applied to the sclera for 5 minutes.
- We did not find any RCTs of 5FU in patients at high risk of surgical failure. RCT evidence for the intraoperative use of 5-FU is limited to low risk patients undergoing primary trabeculectomy.
- Patients undergoing surgery for the first time treated with intraoperative 5-FU had a lower risk of failure at 12 months, than those treated with placebo/no intraoperative treatment. There were 9 fewer failures per 100 (from 3 to 15 fewer) with 5-FU compared to placebo/no intraoperative treatment. There were 96/359 failures (27%) with placebo/no treatment vs 63/352 failures (18%) with 5-FU. ARR 9% NNT 11 (95% CI 7 to 37), to prevent one surgical failure. RR 0.67 (95% CI 0.51 to 0.88, 4 trials, n= 711 participants, high certainty of evidence)
- Intraoperative use of 5-FU in patients undergoing surgery for the first time, reduced mean intraocular pressure (IOP) compared to placebo/no intraoperative treatment. The mean difference in intraocular pressure was -1.04 mm Hg (95% CI -0.43 to -1.65) when comparing patients receiving 5-FU to those receiving placebo/ no intraoperative treatment. This small difference may not be clinically significant.
- The systematic review did not find an increased risk of sight-threatening complications with 5-FU, however other complications such as hypotonous maculopathy and epithelial toxicity were more common with 5-FU.

MMC versus 5 FU

- In patients at high risk of surgical failure (intraoperative and postoperative use, any application method), MMC resulted in fewer surgical failures at 12 months. There were 19/139 failures (14%) with MMC vs 34/125 failures (27%) with 5-FU. ARR 14% NNT 7 (95% CI 4 to 26 fewer with MMC). RR 0.49 (95% CI 0.22 to 1.08, 5 trials, n= 264 participants, low certainty of evidence)
- In patients at low risk of surgical failure (intraoperative and postoperative use, any application method), MMC resulted in fewer surgical failures at 12 months. There were 9/181 failures (5%) with MMC vs 14/189 failures (7%) with 5-FU. ARR 2% NNT 41 (95% CI 13 fewer to 37 more with MMC). RR 0.64 (95% CI 0.19 to 2.2, trials, n=370 participants, low certainty of evidence.
- In a subgroup analysis of patients who were treated with either MMC or 5-FU with an intraoperative sponge application, MMC resulted in fewer surgical failures at 12 months. There were 10/167 failures with MMC vs 17/154 failures with 5-FU. ARR 5% NNT 20 (95% CI 9 fewer to 89 more with MMC). RR 0.52 (95% CI 0.13 to 2.08, 4 trials, n= 321 participants, low certainty of evidence).
- Local management of patients with a failed trabeculectomy involves follow up surgery with the use of Ahmed valves (local cost R5500 – R7200 per valve). Utilizing a NNT of 20, the cost of treating 20 patients with intraoperative sponge application of MMC is R5000 to prevent 1 additional surgical failure which translates to a cost aversion of R5500-7200 for an Ahmed valve (excluding other related surgical costs).

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	
Recommendation: The committee suggests that adult patients with glaucoma undergoing filtration surgery (trabeculectomy) should receive intraoperative mitomycin compared to No mitomycin-C, No 5-fluorouracil, placebo or sham *(conditional, low certainty of evidence).* *Rationale: Intraoperative sponge application of MMC results in fewer surgical failures at 12 months compared to No mitomycin-C, No 5-fluorouracil, placebo or sham. The benefits of 5-FU versus placebo or control is limited to low risk patients only. Furthermore, while the cost per unit of MMC is greater than 5-FU, utilizing an ARR 5%, (NNT 20) for MMC versus 5-FU, the cost of treating 20 patients with intraoperative sponge application of MMC is R5000 to prevent 1 additional surgical failure that would result in a cost of R5500-7200 being averted for an Ahmed valve which is used in follow up surgery, as the current standard of care for patients with failed trabeculectomies.* **Level of Evidence:** MMC vs placebo or no antimetabolite (moderate certainty evidence) and MMC v 5-FU (low certainty of evidence **Review indicator: New evidence on efficacy or safety of MMC**					
NEMLC RECOMMENDATION (MEETING OF 30 November 2023): NEMLC supports the ERC's recommendation as stated above.					
Monitoring and evaluation considerations					
Research priorities					

Authors: G Thom, Z Adam, M McCaul
Author affiliation and conflict of interest details
G Thom, Amajuba DCST, KZN Department of Health.
Z Adam, Consultant for Right to Care.
M McCaul, Centre for Evidence-based Health Care, Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. SA GRADE Network

Acknowledgements
This publication/review was supported by the SA GRADE Network, which is jointly led and managed by Centre for Evidence Based Health Care (CEBHC), Stellenbosch University and the Health Systems Research Unit, South African Medical Research Council

INTRODUCTION/BACKGROUND

Glaucoma is a mixed group of eye disorders with related optic neuropathy (Marais A et al., 2017). While the pathophysiology of glaucoma is not well understood (Schellack N et al., 2017), glaucoma is reported to be responsible for 30% of blindness, the second leading cause of blindness worldwide after cataracts (Cook, 2009). In Africa, glaucoma is said to account for 15% of blindness with the highest incidence and prevalence of blindness relative to other regions worldwide (Baboolal SO et al, 2018).

Glaucoma can present as either a primary inherited disorder or as secondary disorder as a result of trauma, adverse effects to medicines, concomitant disease or congenital abnormalities. Patients may present with open angle glaucoma in which the trabecular meshwork remains open but undergoes morphological changes that results in impaired drainage of intraocular fluid, or closed angle glaucoma in which the pupil of the eye compresses the drainage canal between the iris and cornea, resulting in a raised intraocular pressure (Marais A et al., 2017). Primary open angle glaucoma is cited as being the most common presentation (Marais A et al., 2017) (European Glaucoma Society, 2021).

The number of people with glaucoma was estimated to be 76 million in 2020 worldwide (European Glaucoma Society, 2021), and based on global incidence reports, glaucoma has been suggested to have an ethno-genetic disease pattern (Kapetanakis VV et al, 2016). The overall prevalence of glaucoma in South Africa is stated at 4.5% (Baboolal SO et al, 2018), with estimates of 5 to 7% in the black population and 3 to 5% in the white population (Schellack N et al., 2017). Primary open angle glaucoma is most prevalent in black populations with Asian ethnicity being a risk factor for the less common angle closure glaucoma. A local study by (Salmon JF et al, 1993) conducted in Mamre, a village near Cape Town with strong ancestry links to Southeast Asians, identified primary angle closure glaucoma as a significant public health problem in the Western Cape Province.

The lowering of intra-ocular pressure (IOP) is the only modifiable risk factor in the management of glaucoma and has been considered to be part of established clinical practice over a century ago (Wilkins M et al., 2005), although good evidence in support of this intervention has only more recently been demonstrated (Kass MA et al, 2002) (Heijl a et al, 2002). A systematic review by (Maier PC et al, 2005) concluded that lowering IOP in patients with glaucoma significantly delays visual field deterioration (Hazard ratio =0.65, 95% CI (0.49 to 0.87), P = 0.003; NNT = 7). According to (Marais A et al., 2017), *"the goal of treatment in treating POAG (primary open angle glaucoma) is to establish and maintain the intraocular pressure at a range where visual field loss will have the least negative impact on the patient's perceived visual disability."* In view of the relatively poor sensitivity of measuring intraocular pressure, nearly half of patients with primary open angle glaucoma will present with an IOP below 22mmHg – IOP targets therefore require patient individualization.

Treatment of glaucoma includes pharmacological management, laser therapy or surgery. A Cochrane review by (Burr J et al, 2012) concluded that in severe open angle glaucoma, surgery lowered IOP significantly more than medications (pilocarpine, an older drug not currently widely used) and reduced the risk of progressive loss of visual field. Furthermore, a longitudinal follow up of a sub-group of patients enrolled in the Collaborative Initial Glaucoma Treatment Study (CIGTS) (Gillespie B et al, 2003), 9 years after treatment initiation concluded that initial surgery was beneficial for participants with more advanced visual field loss at presentation but detrimental for patients with diabetes (Musch DC et al, 2009).

Trabeculectomy is the most common type of surgery for glaucoma management and involves the drainage of fluid through surgical incision at the wall of the eye, creating a fistula that drains aqueous humour from the eye to the subconjunctival space thus creating a filtering bleb. Trabeculectomy is cited as the surgery of choice in African eyes even though the risks of failure of filtration blebs is well documented (Cook, 2009). Adjunctive therapy with antimetabolites (mitomycin C and 5 fluorouracil) is reported to be effective in managing the risks of bleb failure through a reduction in postoperative scarring. A negative consequence to inhibiting wound healing is that the conjunctiva overlying the sclerostomy may become very thin, and during the early postoperative period, greater flow of aqueous through the sclerostomy could lead to hypotony. Over time, holes can form in the conjunctiva with bacterial infection resulting in endophthalmitis (Wilkins M et al., 2005).

While mitomycin C is used routinely in clinical practice as an adjunct during trabeculectomy there is no Standard Treatment Guideline for trabeculectomy with no suitable alternative listed on the Essential Drug List. The aim of this review is to assess the efficacy and safety of the use of two commonly used antimetabolites (mitomycin C and 5 fluorouracil) used as adjunctive therapy during trabeculectomy to reduce bleb failure.

ELIBILITY CRITERIA FOR REVIEW

Research Question: Should intraoperative antimetabolites (either MMC or 5-FU) be used in adult patients undergoing trabeculectomy?

Table 1: Purpose/Objective i.e., PICO

Population	Adult patient ≥18 years with glaucoma undergoing filtration surgery (trabeculectomy)
Intervention	Intraoperative mitomycin-C (topical) or 5-fluorouracil (5-FU)
Control	No mitomycin-C, No 5-fluorouracil, placebo or sham
Outcomes	Trabeculectomy failure, change in intraocular pressure (pre- vs post-surgery), need for repeat surgery, adverse events and adverse reactions.
Study designs	Systematic reviews of RCTs or RCTs. Observational studies will only be sourced if the latter are unavailable.

METHODS:

a. Data sources:

The websites of organisations identified by local experts as credible authorities for guideline development (NICE, European Society of Ophthalmology, Royal College of Ophthalmologists, American Academy of Ophthalmology) were searched for relevant guidelines. Additionally, a free text google search was undertaken to identify clinical guidelines/reviews from recognized clinical bodies/authorities within the ophthalmology specialty. Systematic reviews (SRs) of randomised controlled trials (RCTs) were sought in PubMed, the Cochrane Library, and Epistemonikos.

b. Search strategy:

A search for systematic reviews and meta-analyses was conducted on the 2nd August 2023 from the following databases

COCHRANE: mitomycin AND glaucoma yielded 28 results and fluorouracil and glaucoma yielded 21 results

PUBMED: See Appendix 1 for the Pubmed search history which yielded 28 results

EPISTEMONIKOS: mitomycin AND glaucoma yielded 28 results and fluorouracil and glaucoma yielded zero results

c. Screening, data extraction and analysis, evidence synthesis:

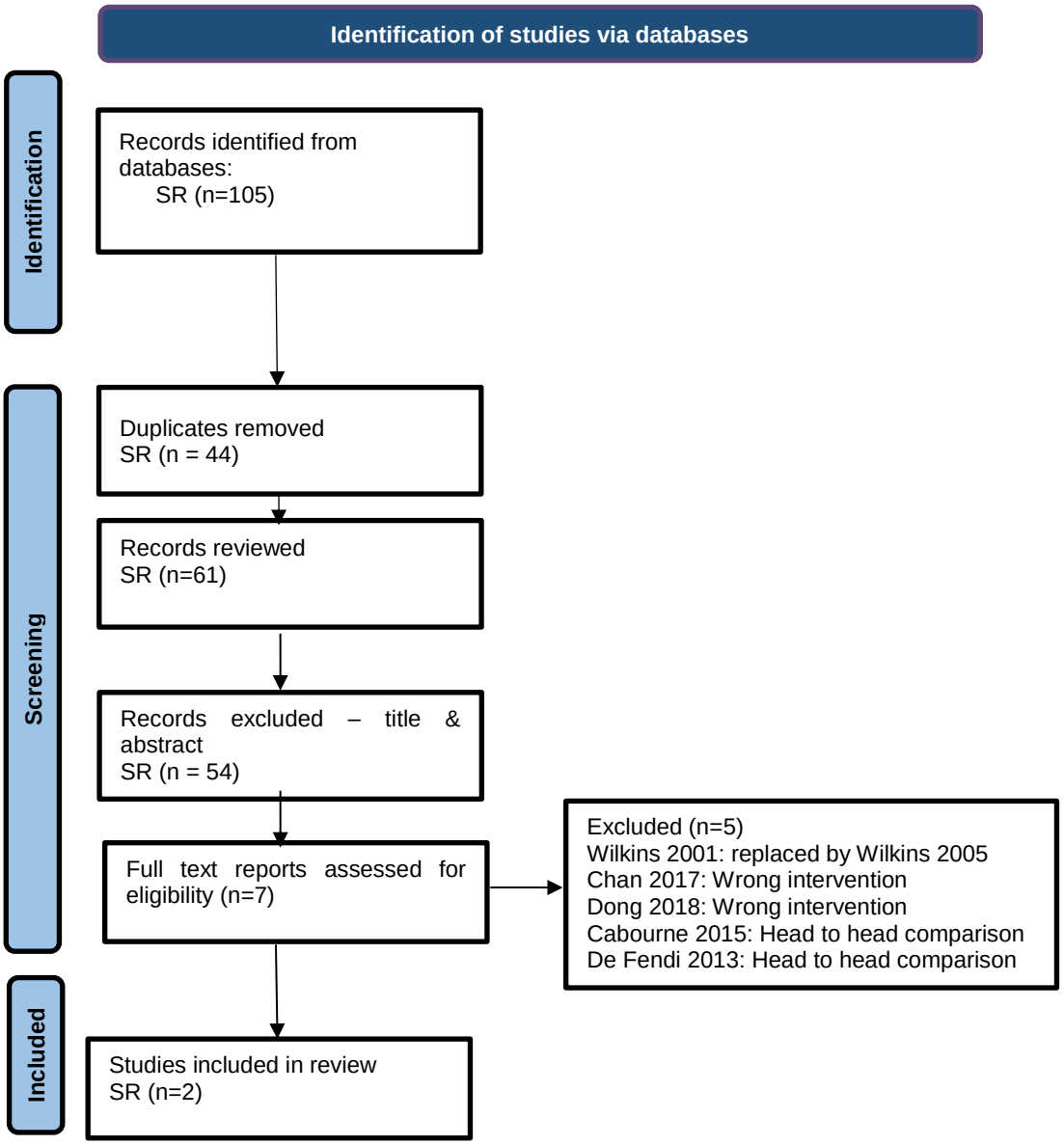
Titles and abstracts were screened independently (ZA) with a second check by (GT). Full text screening was by (ZA) with second checks by (GT). Eligible clinical guidelines were appraised with the AGREE II tool and eligible systematic reviews were appraised using the AMSTAR II Checklist independently by two reviewers (ZA and GT), with discrepancies resolved following discussion.

RESULTS

a. Search Results

Refer to Figure 1 below the Prisma flow diagram. Following removal of duplicates, 61 records were reviewed by title and abstract, with 54 being excluded as not aligned to the PICO. Studies involving congenital glaucoma, non-penetrative procedures (e.g. trabeculoplasty) or trabeculectomy involving cataract surgery or other procedures were excluded. The full text references of 7 studies were assessed for eligibility and a further 5 references were excluded as not specific to our PICO.

Figure 1: Prisma flow diagram



Modified From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

The following SRs were identified for inclusion in the review:

- (Wilkins M et al., 2005) Intraoperative Mitomycin C for glaucoma surgery.
- (Green E et al., 2014) 5-Fluorouracil for glaucoma surgery.

DESCRIPTION OF CLINICAL GUIDELINES, SYSTEMATIC REVIEWS AND RCTs IDENTIFIED

a. Guidelines

Six guidelines were assessed and the key recommendations as relevant to our PICO are summarised in Table 1 below, which includes the AGREE II scores for each.

Table 1. AGREE II assessments of guidelines

Guideline citation and website	Recommendations	AGREE II Appraisal
Glaucoma: diagnosis and management (Jan 2022) (National Institute for Health and Care Excellence (NICE), 2022)	Mitomycin-C is an antimetabolite used during the initial stages of trabeculectomy to prevent excessive postoperative scarring and therefore reduce the risk of failure. NICE recommendations: Treatment for people with advanced COAG • Offer people with advanced COAG, glaucoma surgery with pharmacological augmentation (MMC) as indicated. Give them information on the risks and benefits of surgery. Treatment for people with Chronic open angle glaucoma (COAG) (Use of mitomycin-C off label). Indicated for the following: • Treatment for people with advanced COAG: Offer people with advanced COAG, glaucoma surgery with pharmacological augmentation (MMC) as indicated. Give them information on the risks and benefits of surgery • An option for people with good medication adherence and instillation technique with eye drops where IOP not sufficiently reduced to prevent progression of sight loss • An option for people with COAG who are at risk of progressing to sight loss despite treatment with medicines from 2 therapeutic classes • An options for people with COAG who cannot tolerate a pharmacological treatment -after treatment with medicines from 2 therapeutic classes has been trialed	83
(American Academy of Ophthalmology: Preferred Practice Pattern Glaucoma Committee:, 2020)	A 2005 Cochrane Systematic Review concluded that antifibrotic agents may be used intraoperatively and postoperatively to reduce the subconjunctival scarring after trabeculectomy that can result in failure of the operation, and therefore intraoperative MMC should be used. (I+, Moderate Quality, Strong Recommendation) Studies confirm this outcome in eyes at high risk of surgical failure and eyes that have not undergone previous surgery. A 2015 Cochrane Systematic Review concluded that there is low quality evidence that MMC may be more effective than intraoperative 5-fluorouracil (5- FU) in achieving long-term lower IOP. A 2014 Cochrane Systematic Review reported evidence that intraoperative 5-FU may improve the success rate of lowering IOP compared with no antifibrotic agents but requires multiple injections. Also, 5-FU is increasingly being used on an ad-hoc basis, for which there is no evidence. Therefore, the selection of intraoperative MMC or 5-FU should be left to the discretion of the treating ophthalmologist, in consultation with the individual patient. Intraoperative 5-FU and MMC were found to be equally safe and effective adjuncts to primary trabeculectomy in a multicenter, randomized clinical trial. The use of postoperative injections of 5-FU also reduces the likelihood of surgical failure in both high-risk eyes and eyes that have not undergone previous surgery. A 2014 Cochrane Systematic Review reported that postoperative injections of 5-FU were rarely utilized in postoperative regimens, perhaps because of patient preference and an increased risk of complications. Thus, the routine administration of postoperative 5-FU is not recommended, but should be based on individualized considerations for the patient.457 (I++, Moderate Quality, Strong Recommendation) . The use of an antifibrotic agent carries with it an increased risk of complications such as hypotony, hypotony maculopathy, late-onset bleb leak, and late-onset infection that must be weighed against the benefits when deciding whether to use these agents. These complications may be even more common in primary filtering surgery of phakic patients. A trend toward a lower concentration and shorter exposure time of MMC has been observed over time, and use of a fornix-based conjunctival flap with broad application of MMC has been advocated to avoid bleb-related complications.	75
Management of angle closure glaucoma guidelines (The Royal College of Ophthalmologists, 2022)	In medically uncontrolled **primary angle-closure glaucoma (PACG)** eyes without cataract, trabeculectomy with mitomycin C may be indicated, particularly in younger patients with accommodative ability. In a small RCT comparing the efficacy of phacoemulsification versus trabeculectomy with mitomycin-C in medically uncontrolled PACG eyes with clear lens, trabeculectomy group was found to be more effective than phacoemulsification, requiring on average 1.1 fewer drugs after surgery. Surgical complications were substantially higher in the trabeculectomy group than among those undergoing phacoemulsification (44% vs. 4% respectively). There were no differences between the two treatment groups in number of additional surgical interventions at 2 years, although one third of patients undergoing trabeculectomy developed significant cataract within this timeframe. However, in cases of advanced PACG, uncontrolled IOP and concurrent cataract, primary trabeculectomy with mitomycin-C may be a viable option. The sequence of cataract and glaucoma	75

	surgery need to be considered carefully. The benefits of sequential surgery versus combined phaco-trabeculectomy in more severe or advanced disease remain unclear.	
Terminology and guidelines for glaucoma. (European Glaucoma Society, 2021)	Antifibrotics such as 5-fluorouracil (5-FU) and mitomycin-C (MMC) are routinely used in patients undergoing glaucoma filtration surgery in order to reduce postoperative conjunctival scarring and improve drainage. Although 5-FU and MMC are not officially approved for ocular surgery, their off-label use in filtration surgery has become standard clinical practice and there is evidence supporting their use. The use of antifibrotics is potentially hazardous, and requires careful surgical technique to prevent complications. Early and late over drainage and hypotony, or a thin focal drainage bleb that is associated with a higher risk of infection, are more common with antifibrotics. The use of larger antifibrotic treatment areas and a fonix-based conjunctival flap may minimize the occurrence of thin cystic blebs. It is important to assess each individual case for risk factors, and/or for the need of low target IOP and choose the substance, concentration, volume and duration of exposure used. The use of antifibrotics will enhance the unfavourable effect of any imprecision during surgery. Administration 5-Fluorouracil: – Intraoperative use – Concentration: 25 or 50 mg/ml undiluted solution. Administration: on a filter paper or a sponge or by subconjunctival injection. – Time of exposure: usually 5 minutes. Rinse: with at least 20 ml of balanced salt solution. Mitomycin C: – Intraoperative use – Concentration: 0.1-0.5 mg/ml – Administration: intraoperatively on a filter paper or a sponge or by subconjunctival injection. – Time of exposure: 1-5 minutes if on a filter paper or sponge. – Rinse: with at least 10-20 ml of balanced salt solution.	58
(**Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline** Expert Committee; Canadian Ophthalmological Society., 2009)	The use of perioperative locally applied antimetabolites has improved success rates, particularly in eyes at risk for failure. Postoperative 5-fluorouracil injected subconjunctivally was initially studied in a randomized prospective fashion with improved success in the group receiving the 5-fluorouracil and subsequently found to improve surgical success rates in several studies. 5-fluorouracil has largely been replaced by mitomycin C, which is a more potent antiscarring agent that can be applied in a more convenient fashion intraoperatively. Although antimetabolites do increase the success of trabeculectomy, they may also increase the risk of postoperative complications including wound leak, hypotony suprachoroidal hemorrhage, and bleb-related endophthalmitis.	42
The Japan Glaucoma Society guidelines for glaucoma 5th edition 2023 (Kiuchi Y et al, 2023)	Trabeculectomy This technique adjusts the filtration rate by fabricating a scleral flap, excising the limbus tissue below the scleral flap, and suturing the scleral flap. It is currently the most common glaucoma surgery for most types of glaucoma, including primary open-angle glaucoma (broad). The antimetabolic agents, mitomycin C or 5-fluorouracil are used intraoperatively and postoperatively to inhibit scarring at the filtration site.	42

b. Systematic reviews and randomised controlled trials

- ***Systematic review:***

Table 2. AMSTAR 2 assessment of the SRs

Systematic review	Conclusions	AMSTAR 2 appraisal
(Wilkins M et al., 2005) Intraoperative Mitomycin C for glaucoma surgery.	Intraoperative MMC reduces the risk of surgical failure in eyes that have undergone no previous surgery and in eyes at high risk of failure. Compared to placebo it reduces mean IOP at 12 months in all groups of participants in this review. Apart from an increase in cataract formation following MMC, there was insufficient power to detect any increase in other serious side effects such as endophthalmitis. It is possible that low event rates and varying definitions would prevent the detection of a true increase in complications such as infection and hypotony. The quality of evidence supporting these conclusions is at best moderate and often low.	Low quality review
(Green E et al., 2014) 5-Fluorouracil for glaucoma surgery.	This SR assessed the effects of both intraoperative application **and postoperative injections** of 5-FU in eyes of people undergoing trabeculectomy. (note that postoperative application of antimetabolites is outside the scope of our PICO).	Low quality review

	Postoperative injections of 5-FU are now rarely used as part of routine packages of postoperative care but are increasingly used on an ad hoc basis. This presumably reflects an aspect of the treatment that is unacceptable to both patients and doctors. None of the trials reported on the participants' perspective of care, which constitutes a serious omission for an invasive treatment such as this. The small but statistically significant reduction in surgical failures and intraocular pressure at one year in the primary trabeculectomy group and high-risk group must be weighed against the increased risk of complications and patient preference.	

MMC (Wilkins M et al., 2005)

The Cochrane review by (Wilkins M et al., 2005), considered the use of intraoperative mitomycin C compared to placebo as an adjunct in trabeculectomy surgery as a treatment for glaucoma. The SR included 11 RCTS with a total of 698 participants. The trials enrolled three types of participants (see Appendix 5). RCTs that were included in the review involved the use of intraoperative MMC at any concentration and dose (studies included doses that ranged from 0.1 to 0.5 mg/mL saline over 1 to 5 minutes) compared to placebo or control. The primary outcomes focused on the efficacy of MMC and was assessed as the proportion of failed trabeculectomies at 12 months after surgery and the mean IOP at 12 months after surgery. Failure was defined as repeat surgery or uncontrolled IOP (usually more than 22 mmHg) despite additional topical or systemic medications. Secondary outcomes focused on adverse effects which included wound leaks, hypotony, late endophthalmitis, expulsive haemorrhage, shallow anterior chamber and cataracts.

5-FU (Green E et al., 2014)

The Cochrane review by (Green E et al., 2014) was an update of a previous Cochrane review first published in 2000 with an update in 2009, that assessed the *postoperative* use of 5FU (not covered by our PICO) compared with control following trabeculectomy. Since the 2000 publication, new evidence on the use of intraoperative 5FU was published and the review authors took the decision to expand the scope of the original review to include intraoperative use of 5FU. For the purposes of the review, the interventions were divided into three subgroups of 5FU injections (intraoperative, regular dose postoperative and low dose postoperative) and participants were categorized into 3 subgroups (see Appendix 5). The review includes 12 RCTS encompassing 1319 participants, of which 5 trials that included a total of 770 participants involved the **intraoperative use of 5FU in patients undergoing primary trabeculectomy** - we have limited our reporting to the use of intraoperative 5FU only, in accordance with our pre-specified PICO. Intraoperative use of 5-FU included administration of moistened sponges with either 25mg/mL or 50mg/mL to the sclera for 5 minutes. The primary outcomes were the proportion of failed trabeculectomies at 12 months after surgery, and the mean IOP at 12 months. Secondary outcomes were reported as adverse event rates and included wound leaks, hypotony, late endophthalmitis, expulsive haemorrhage, shallow anterior chamber, corneal and conjunctival epithelial erosions and other complications.

- ***Randomised controlled trials:***

The Medline search for RCTs by (Wilkins M et al., 2005) was done until January 2010 and for (Green E et al., 2014) until July 2013. We conducted a further Pubmed search for relevant RCTs involving MTC and 5-FU since the literature search by (Wilkins M et al., 2005) and (Green E et al., 2014) respectively, to identify any updates since.

The following RCT was identified as relevant to our PICO:

MMC

(Shaheer M et al, 2018): **Comparison of mean corneal cell loss after trabeculectomy with and without mitomycin C**

Sixty patients with primary open angle glaucoma uncontrolled with medication were identified from an outpatient ophthalmology department in Pakistan to undergo trabeculectomy with (Group A) or without MMC (Group B). The objective of the study was to assess mean endothelial cell loss with or without MMC. Endothelial cell loss is a concern because the corneal endothelium is a monolayer of cells which play an important role in corneal hydration and transparency. Disruption to this layer of cells has a critical impact on physiological function, negatively impacting the drainage of intraocular fluid and corneal transparency which could lead to irreversible corneal oedema and blindness. These cells have limited replicative ability in vivo.

Additional RCTS that compared different doses of MMC and different surgical techniques using MMC were also identified. These were not deemed directly relevant to our PICO so have not been summarised in our results, however, relevant mention of these studies is included as part of our conclusion.

OUTCOMES

EFFECTIVENESS:

MMC (Wilkins M et al., 2005)

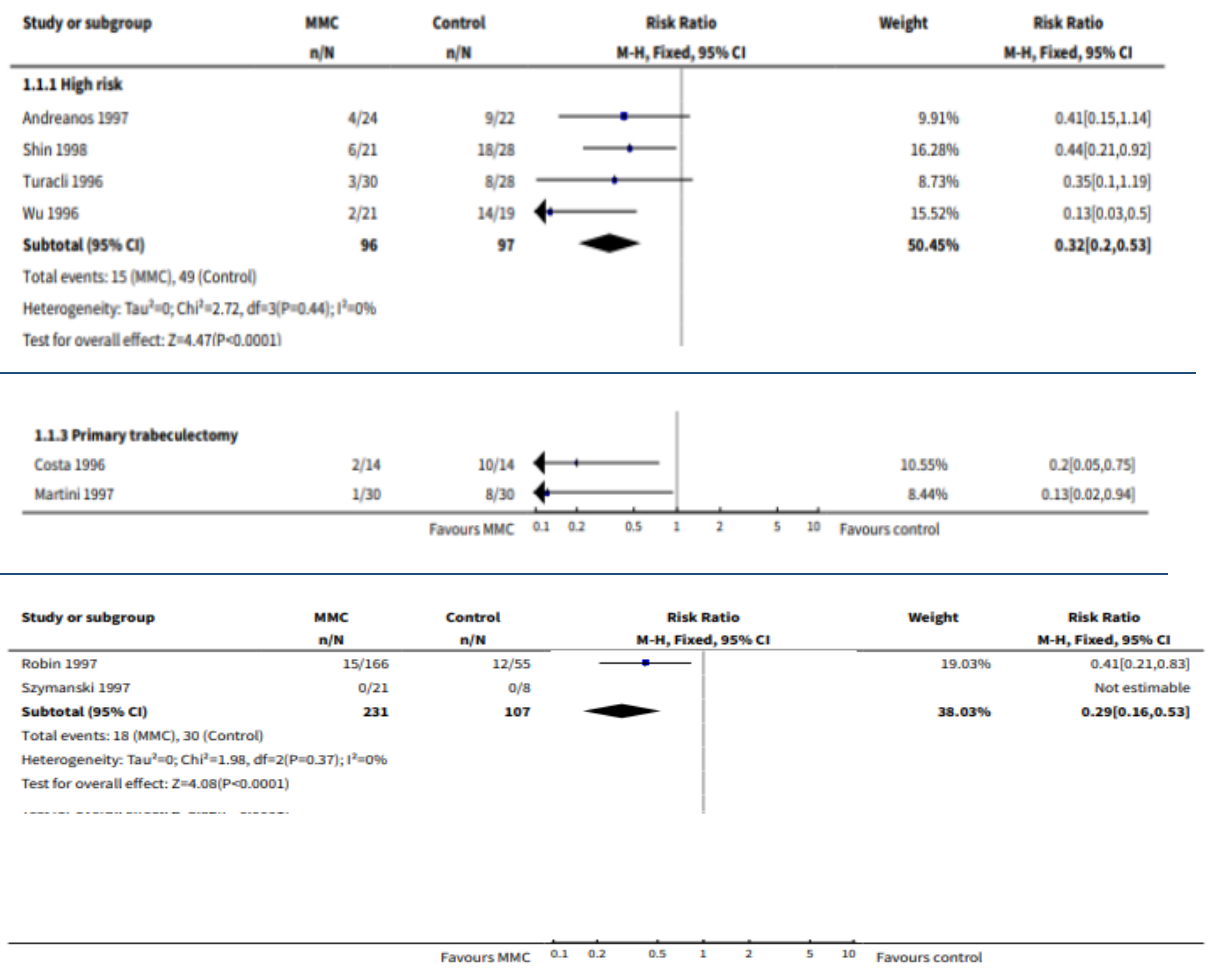
Refer to Appendix 2 for the summary of findings table for **Intraoperative Mitomycin C compared with no antimetabolite or placebo** for trabeculectomy surgery for glaucoma

Failure at 12 months:

High risk of failure group, Intraoperative MMC demonstrated a protective benefit against failure of surgery at 12 months (RR 0.32, 95% CI 0.20 to 0.53, 4 trials, n= 193 participants, moderate certainty of evidence) when compared to placebo/no intraoperative treatment, resulting in 35 fewer per 100 (from 22 to 46 fewer) surgical failures.

Primary trabeculectomy group: MMC demonstrated a 71% reduction in risk of surgical failure (RR 0.29, 95% CI: 0.16 to 0.53, 4 trials, n= 338 participants, moderate certainty of evidence) relative to no antimetabolite or placebo, resulting in 20 fewer per 100 (from 12 to 30 fewer) with MMC relative to no antimetabolite or placebo.

Figure 2 : Intraoperative MMC versus control, High risk and primary trabeculectomy – failure at 12 months

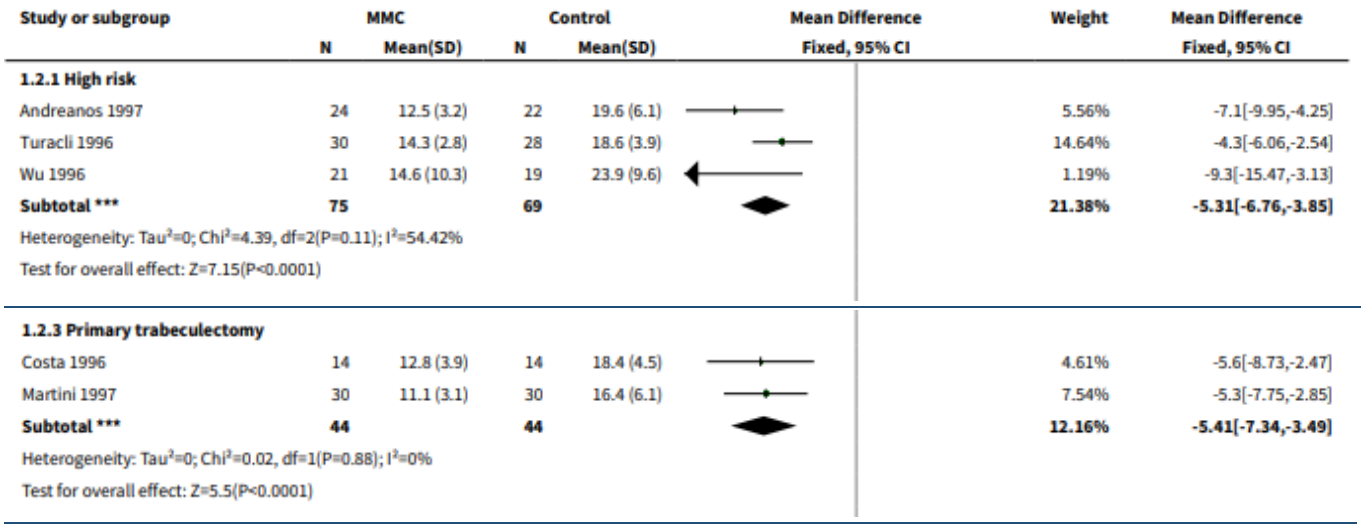


Mean intraocular pressure (IOP) at 12 months

High risk of failure group: Three trials reported that MMC produced a statistically significant reduction in IOP from baseline to 12 months with the weighted mean difference across the 3 trials combined, demonstrating that MMC lowers IOP by 5.31 mmHg more than placebo (95% CI: 3.85 to 6.76 mmHg).

Primary trabeculectomy group: The mean reduction in IOP at 12 months was similar across the 2 trials that reported this outcome, with a pooled estimate of effect favouring MMC over placebo (mean difference in decrease from baseline 5.41 mmHg, 95% CI: 3.48 to 7.34 mmHg).

Figure 3 : Intraoperative MMC versus control, High risk and primary trabeculectomy – mean IOP at 12 months



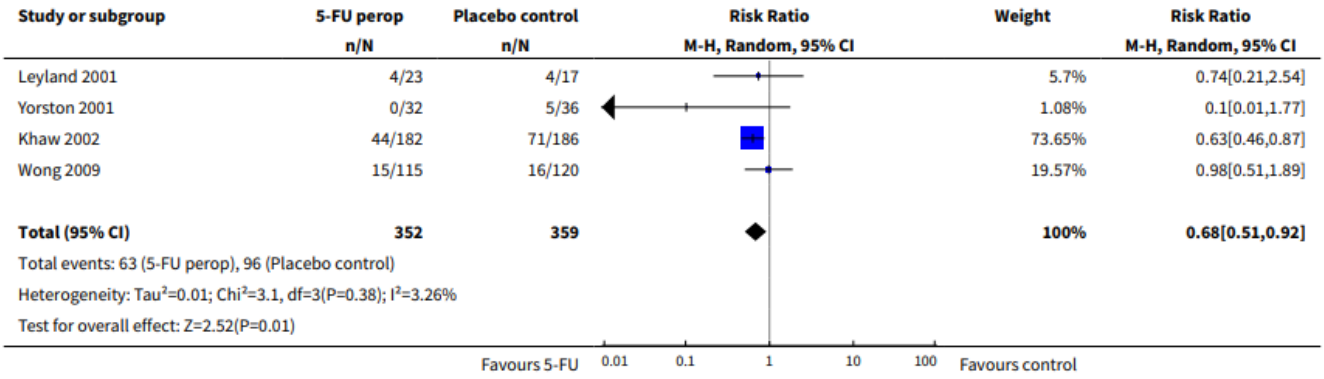
5-FU (Green E et al., 2014)

Refer to Appendix 3 for the summary of findings table for **Intraoperative 5-Fluorouracil versus placebo or control** for glaucoma surgery.

Failure at 12 months:

Primary trabeculectomy group: The reviewers report a substantial point estimate risk reduction of failure at one year of 0.68 (95% CI 0.51 to 0.92, 4 trials, n= 711 participants, high certainty of evidence) with 5-FU than those treated with placebo/no intraoperative treatment, resulting in 9 fewer per 100 (from 3 to 15 fewer) with 5-FU), Results were based primarily on outcomes from the to the Khaw (2002) study. According to the reviewers, the difference in effect estimates of the different trials did not reflect the lower dose of 5- FU used in Leyland 2001 and Yorston 2001.

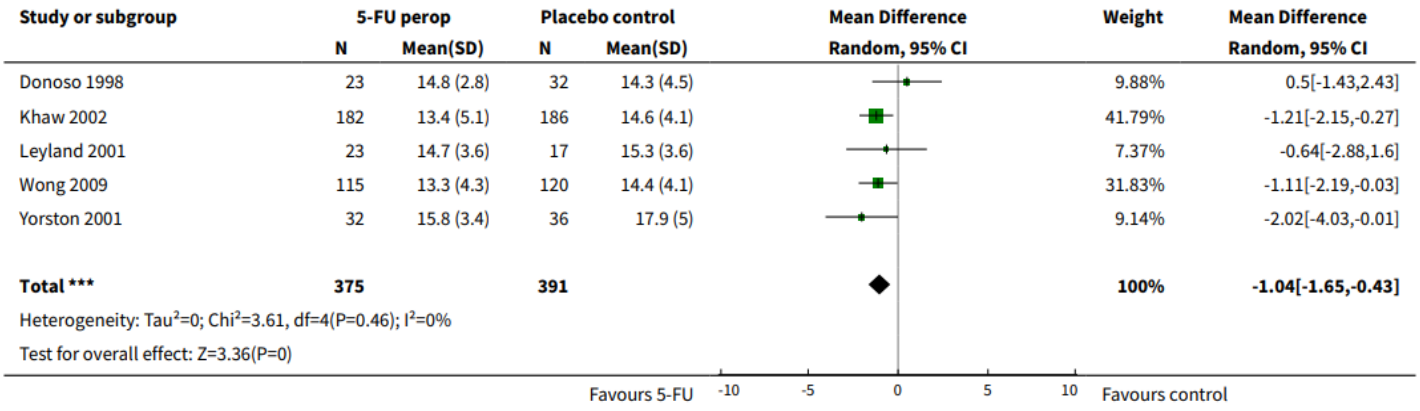
Figure 4 : Regular dose intraoperative 5-FU versus placebo or control, primary trabeculectomy – failure at 12 months



Mean intraocular pressure (IOP) at 12 months

Primary trabeculectomy group: A small overall reduction in IOP of 1.04 mm Hg (95% CI 0.43 to 1.65) was demonstrated which is statistically significantly but may not be clinically significant according to the review authors.

Figure 5 : Regular dose intraoperative 5-FU versus placebo or control, primary trabeculectomy –Mean IOP at 12 months



SAFETY

MMC

MMC (Wilkins M et al., 2005)

Wound leak:

High risk of failure group: No reported events in MMC or placebo groups.

Primary trabeculectomy group: While there were more events in the MMC group compared to placebo in the two studies that reported on this outcome, the difference was not statistically significant.

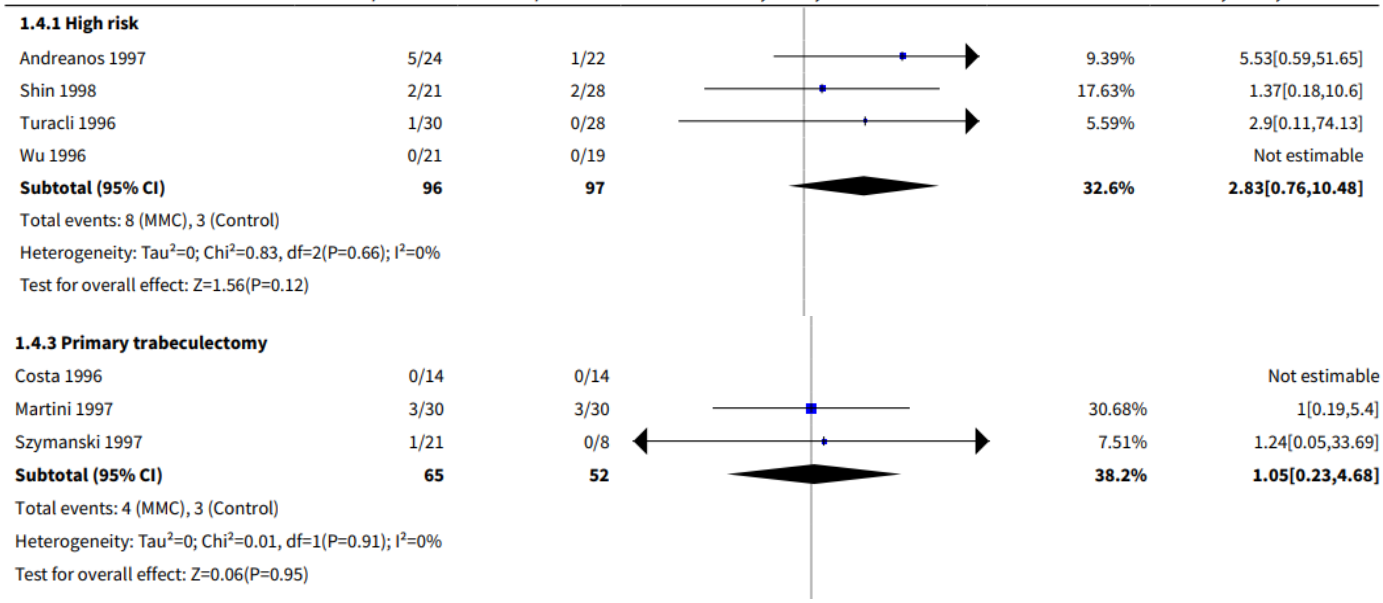
Hypotony:

High risk of failure group: Increased risk of hypotony reported with MMC OR 2.83, 95% confidence interval (CI): 0.76-10.48, 3 RCTs, 193 participants

Primary trabeculectomy group: Increased risk of hypotony reported as OR 1.05 95% confidence interval (CI): 0.23-4.68 RCTs, 117 participants

While the point estimate in all three risk groups show an increase in the risk of hypotony with MMC, the wide confidence intervals for the reported odds ratios in each group all cross 1, hence the results are not statistically significant.

Figure 6 : Intraoperative MMC versus control, Complications - hypotony



Endophthalmitis:

Primary trabeculectomy group: One study reported on this outcome in which no cases of endophthalmitis occurred (0/229 in the MMC group compared to 0/71 in the control group).

Shallow anterior chamber:

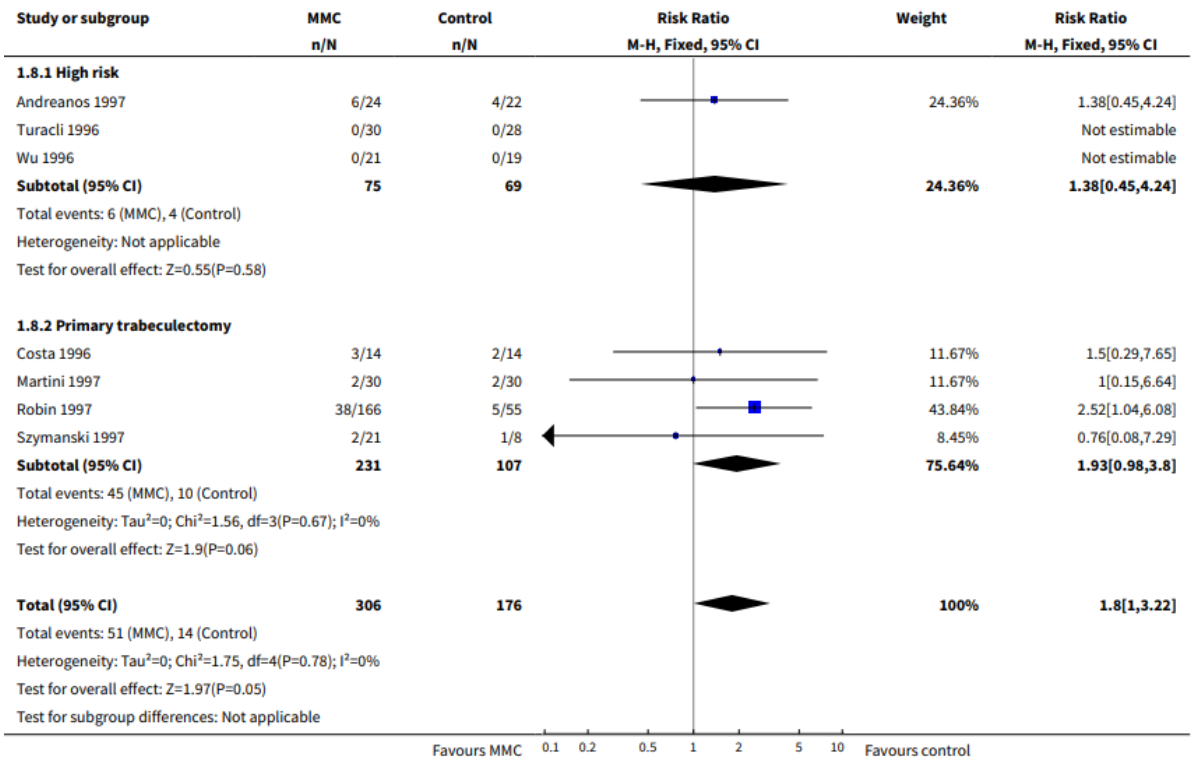
There was no reported difference between MMC and placebo across each of the risk groups and overall. However the rates of occurrence varied markedly from 0/57 to 8/30 across MMC and control groups which the review authors attribute most likely to variation in the definitions used as well as surgical technique.

Cataract:

Primary trabeculectomy group: one study (Robin 1997) reported a statistically significant increase in the risk of cataract associated with the use of MMC. Using a fixed-effect model, the pooled estimates of effect showed that the risk of cataract was possibly increased with MMC use in trials of participants in the primary trabeculectomy group (RR 1.93, 95% CI: 0.98 to 3.80), as well as for all participant groups analysed together (RR 1.80, 95% CI: 1.00 to 3.22).

Cataract was the only side effect that was significantly increased with the use of MMC, with a NNH=15 for one additional cataract.

Figure 7: Intraoperative MMC versus control: Complications – cataract



Endothelial cell loss: (Shaheer M et al, 2018)

The results of this small study (n= 60) demonstrate that the mean endothelial cell loss was three times greater with adjunctive MMC compared to trabeculectomy with no MMC. The median endothelial cell loss in group A was 283.00 (66.50), and in group B the median endothelial cell loss was 72.50 (19.25), which was statistically significant (p<0.001). No cases of corneal decompensation or other complication were noted despite the higher rate of endothelial cell loss.

Figure 8: Endothelial cell loss with and without MMC

Endothelial cell loss	Median	IQR	Minimum	Maximum
With MMC	283.00	66.50	179	356
Without MMC	72.50	19.25	44	105

P-value <0.001 (Mann-Whitney test was used as the data was not normal).

5-FU (Green E et al., 2014)

Figure 9: Risk of complications

Intervention	Complication (risk ratio (95% confidence interval))			
	Wound leak	Hypotonous maculopathy	Shallow anterior chamber	Epithelial toxicity
Primary trabeculectomy	1.36 (1.00, 184)	1.47 (0.42, 5.12)	1.99 (1.22, 3.22)	1.23 (0.85, 1.77)

Wound leak:
5-FU caused a 50% increase in the RR of wound leak, which is just significant with the summary estimate with no statistical heterogeneity or apparent dose-related response.

Hypotonous maculopathy:
Only one study (Khaw 2002) reported on this outcome which was slightly more common with 5-FU.

Late endophthalmitis and expulsive haemorrhage:
These outcomes were not reported in studies using intraoperative 5-FU.

Shallow anterior chamber:
The risk of this side effect was significantly increased with the use of intraoperative 5-FU, however one study (Wong 2002) did demonstrate an opposite risk.

Epithelial toxicity:
Reported as slightly more common with 5-FU in one (Wong 2009) of the two trials that reported on this outcome.

CONCLUSION

- While the use of MMC and 5-FU remain off-label during trabeculectomy, these agents are used routinely during glaucoma filtration surgery to reduce post-operative scarring and improve filtration. The use of antimetabolite agents (MMC and/or 5-FU) is recommended in a number of international clinical guidelines (as detailed above).
- Based on the results of our review, MMC results in a reduction in in surgical failure at 12 months in both low and high risk groups when compared to placebo or no antimetabolite. The absolute risk reduction is greater in patients at high risk of surgical failure compared to patients undergoing surgery for the first time.
- There were no RCTS of 5-FU in high risk patients
- Intraoperative 5-FU results in a small reduction in surgical failure at 12 months when compared to placebo/control in low risk patients undergoing trabeculectomy. The absolute risk reduction was smaller than that achieved with MMC. The magnitude of this benefit must be weighed against the potential risk of complications such as wound leak - RR 1.36 CI 1 to 1.84 (high certainty evidence) and shallow anterior chamber RR 1.99 CI 1.22 to 3.22 (high certainty evidence).
- Neither MMC nor 5-FU increased the risk of significant adverse effects. However studies were small, definitions of adverse effects were heterogeneous and there were no studies reporting on long term adverse effects

MMC v 5-FU
- Our pre-specified PICO does not include a comparison between MMC and 5-FU, however, our original literature search did include 2 SRs of RCTs (Cabourne E, et al., 2015) (De Fendi LI et al., 2013) where head to head comparisons were undertaken. As 5-FU is sometimes used in local clinical practice when there are supply constraints with MMC, we thought it useful to include a brief summary of the outcomes of the head to head comparison. Furthermore, 5-FU injection is considerable cheaper than MMC injection. As the more recent Cochrane review by (Cabourne E, et al., 2015) included all 5 of the RCTS included in (De Fendi LI et al., 2013), we limited our reporting to outcomes from the more recent Cochrane SR by (Cabourne E, et al., 2015).
- The SR by (Cabourne E, et al., 2015), included 11 trials with a total of 679 participants. Like the SRs by (Wilkins M et al., 2005) and (Green E et al., 2014), participants at high and low risk of trabeculectomy failure were included. Differences however are that in the (Cabourne E, et al., 2015) review, the **definition of high risk patients included patients of African origin** (see Appendix 5) which is of relevance for the local context. Another less important

difference in the review by (Cabourne E, et al., 2015) is that none of the studies included patients at medium risk of failure (combined trabeculectomy and cataract surgery), a cohort that is outside the scope of our PICO.

- There was also a high degree of heterogeneity in the application methods of the different interventions i.e. while the majority of studies for MMC used an intraoperative sponge application, one study used intraoperative subconjunctival injection).The doses of MMC used also varied between studies (see Appendix 4). The reviewers conducted a dose–response analysis which demonstrated a trend that increasingly favoured the use of MMC versus 5-FU as the intraoperative exposure to MMC increased. For 5-FU, studies varied between intraoperative and postoperative use (doses for postoperative injection varied) as well as between intraoperative sponge technique and subconjunctival injection. An analysis on the method of 5FU administration revealed that there was no significant effects on the overall outcome whether 5-FU was administered by postoperative subconjunctival injections or by intraoperative sponge application (subgroup difference P=0.93).
- (Cabourne E, et al., 2015) concluded that risk of failure of trabeculectomy was lower with MMC compared to 5-FU (RR=0.54, 95% CI 0.30 to 1.00; studies = 11; I^2=40% for the overall cohort (***intraoperative and postoperative use of MMC and 5-FU*** *and any administration method*). This translates to an ARR of 7 fewer per 100 (from 2 to 13 fewer) with MMC, however the confidence interval is wide and crosses the line of no effect. Overall, there was no evidence for any difference between the high and low risk groups (test for subgroup differences P=0.69) but due to the small number of trials in each group, the analysis was insufficiently powered to detect any differences. Refer to Appendix 4 for a more detailed **sub-group analysis focussing on the intraoperative sponge application which would be in line with local practice..**
- In the overall cohort (*intraoperative and postoperative use of MMC and 5-FU and any administration method)*, people treated with MMC had a lower IOP at one year compared to 5-FU (mean difference -3.05mmg Hg, 95% CI-4.60 to -1.50; I^2=52% [*inconsistency between trials with large range in the mean difference between studies]).* As illustrated in table 3 below, the mean difference was greater in the high risk group compared to the low risk group but according to the review authors, the test for interaction was not statistically significant (P=0.11).
- The reviewers report that adverse events were relatively rare with imprecise estimates of effect. Refer to Appendix 6 for a detailed list of the estimates of effect for the reported adverse effects. There is some evidence of less epitheliopathy (RR 0.23, 95% CI 0.11 to 0.47) and less hyphaema (RR 0.62, 95% CI 0.42 to 0.91) in the MMC group.
- The reviewers graded the quality of the evidence as low due to the risk of bias in the included studies and imprecision in the estimate of effects. (See Appendix 7 for the SoF table).
- In their evaluation of post-op complications, (Cabourne E, et al., 2015) reported a higher incidence of epitheliopathy and hyphaema with 5-FU compared to MMC. However, MMC was reported to have been associated with more bleb leaks, wound leaks, late hypotony and cataract formation versus 5-FU. The authors of the SR reported the quality of evidence to be low and caution against drawing any definitive conclusions given that adverse outcomes were rare.
- (Cabourne E, et al., 2015) concluded that MMC may be a more effective antimetabolite compared to 5-FU in achieving a lower IOP following trabeculectomy for both high and low risk sub-groups based on low quality evidence.
- Local management of patients with a failed trabeculectomy involves follow up surgery with the use of Ahmed valves (local cost R5500 – R7200 per valve) – refer to Table 3 for further comment.

Table 3: Outcomes of meta-analysis completed by (Cabourne E, et al., 2015)

Description of Analysis MMC vs 5-FU	Risk Ratio M-H, Random 95% CI	ARR	Excluding trials at high risk of bias in 1 or more domains***	Comparative cost of Ahmed valve due to surgical failure
Outcome: Failure of functioning trabeculectomy at one year (INTRAOPERATIVE & POSTOPERATIVE USE, ANY APPLICATION METHOD)				
High risk of failure**	**0.49 (0.22-1.08)**	Total events MMC = 19/139 Total events 5-FU = 34/125 ARR = 14% NNT= 7 95% CI 4 to 26 **14 fewer per 100 (from 4 to 26 fewer) with MMC**		The cost of treating 7 high risk patients with MMC is R1750 to prevent 1 additional surgical failure which would cost R5500-R7200 for an Ahmed valve (excluding other surgical costs).
Low risk of failure	0.65 (0.19-2.2)	Total events MMC = 9/181 Total events 5-FU = 14/189 ARR = 2% NNT = 41 95% CI -37 to 13 **2 fewer per 100 (from 8 fewer to 3 more) with MMC**		The cost of treating 41 low risk patients with MMC is R10 250 to prevent 1 additional surgical failure which would cost R5500-7200 for an Ahmed valve (excluding other surgical costs)
Overall	0.54 (0.3-1)	Total events MMC = 28/302 Total events 5-FU = 48/292 ARR = 7% NNT = 14 95% CI 8 to 56 **7 fewer per 100 (from 2 to 13 fewer) with MMC**	RR 1.02, 95% CI 0.5 to 2.04	
Outcome: Failure of functioning trabeculectomy at one year (SUBGROUP: INTRAOPERATIVE SPONGE APPLICATION)				
Overall	0.52 (0.13-2.08)	Total events MMC = 10/167 Total events 5-FU = 17/154 ARR = 5% NNT = 20 95% CI -89 to 9 **5 fewer per 100 (from 12 fewer to 1 more) with MMC**		The cost of treating 20 patients with MMC is R5000 to prevent 1 additional surgical failure which would cost R5500-7200 for an Ahmed valve (excluding other surgical costs)
Outcome: Intraocular pressure at 1 year (INTRAOPERATIVE & POSTOPERATIVE USE, ANY APPLICATION METHOD)				
High risk of failure**	**-4.188 (-6.73, -1.64)**			
Low risk of failure	-1.72 (-3.28,-0.16)			
Overall	-3.05 (-4.6, -1.5)		MD -1.72 mmHg, 95% CI -3.28 to -0.16	
*Low risk of trabeculectomy failure: (primary trabeculectomy): people who have received no previous surgical eye intervention. People who underwent previous laser procedures may be included in this group ****High risk of trabeculectomy failure**: people with previous glaucoma or extracapsular cataract surgery, **people of African origin** and people with secondary glaucoma or congenital glaucoma *** Excluding studies at high risk of bias (trials were from the high risk of failure cohort), improved the consistency (reduced I^2), altered the estimate of effect but the generally uncertainty of the results did not change.				

Evidence to decision framework

Should intraoperative antimetabolites (either MMC or 5-FU) be used in adult patients undergoing trabeculectomy?

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** **MMC** High ☐ Moderate X Low ☐ Very low ☐ **5-FU** High X Moderate ☐ Low ☐ Very low ☐ **MMC v 5-FU** High ☐ Moderate ☐ Low X Very low ☐ *High quality: confident in the evidence* *Moderate quality: mostly confident, but further research may change the effect* *Low quality: some confidence, further research likely to change the effect* *Very low quality: findings indicate uncertain effect*	**MMC vs placebo or no antimetabolite** *Surgical failure at 12 months* Moderate quality of evidence (SoF Appendix 2) *Mean IOP* Moderate quality of evidence (SoF Appendix 2) **5-FU vs placebo or control** *Surgical failure at 12 months* High quality of evidence (SoF Appendix 3) *Mean IOP* High quality of evidence (SoF Appendix 3) **MMC v 5-FU** *Surgical failure at 12 months* Low quality of evidence (SoF Appendix 7) *Mean IOP* Low quality of evidence (SoF Appendix7)
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** **MMC** Large ☐ Moderate X Small ☐ None ☐ **5-FU** Large ☐ Moderate ☐ Small X None ☐ **MMC vs 5-FU** Large ☐ Moderate ☐ Small X None ☐ **Overall size of benefit is moderate**	**Intraoperative MMC vs placebo or no antimetabolite** *Surgical failure at 12 months* MMC resulted in a reduction of surgical failure *High risk:* 35 fewer per 100 (from 22 to 46 fewer) with MMC Control 49/97 (50%) failed vs MMC 15/96 (15%) failed, ARR 35%, NNT 3 CI 2 to 5 fewer with MMC to prevent one failed surgery. *Low risk:* 20 fewer per 100 (from 12 to 30 fewer) with MMC Control 30/107 (28%) vs intervention 18/231 (8%) ARR 20%, NNT 5 CI 3 to 9 fewer with MMC to prevent one failed surgery. *Mean IOP at 12 months* MMC reduced mean IOP *High risk:* mean difference of -5.31 mmHg (95% CI: -3.85 to -6.76 mmHg) with MMC *Low risk*: mean difference of -5.41 mmHg, 95% CI: -3.49 to -7.34 mmHg) with MMC. **5-FU vs placebo or control** *Surgical failure at 12 months* *High risk:* No data available *Low risk:* 9 fewer per 100 (from 3 to 15 fewer with 5-FU. There were 96/359 failures (27%) with placebo/no treatment vs 63/352 failures (18%) with 5-FU. ARR 9%. NNT 11 CI 7 to 37 fewer with 5-FU to prevent one surgical failure. *Mean IOP* *High risk:* No data available *Low risk:* mean difference of -1.04 mm Hg (95% CI -0.43 to -1.65) which is statistically significantly but may not be clinically significant. **MMC vs 5-FU**

		Surgical failure at 12 months (Subgroup – intraoperative sponge application only) 5 fewer per 100 (from 12 fewer to 1 more) with MMC, ARR 5% NNT 20 95% CI 9 fewer to 89 more failures. The estimate of NNT is imprecise with wide confidence intervals that cross zero, and therefore include increased harm with MMC *Note that in the Cabourne review, patients from African origin were identified as a high risk cohort which has relevance for our local context, although a sub-group analysis for high risk patients with intraoperative sponge application was not conducted)*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** **MMC** High [ ] Moderate [ ] Low [X] Very low [ ] **5-FU** High [ ] Moderate [X] Low [ ] Very low [ ] **MMC versus 5-FU** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	**MMC vs placebo or no antimetabolite** *Increased risk of wound leak, hypotony and shallow anterior chamber* Low quality of evidence (SoF Appendix 2) *Cataract formation* Moderate quality of evidence (SoF Appendix 2) **5-FU vs placebo or control** *Increased risk of wound leak and shallow anterior chamber* High quality of evidence (SoF Appendix 3) *Epithelial toxicity & hypotonous maculopathy* Moderate quality of evidence (SoF Appendix 3) **MMC versus 5-FU** *Hypotony* Low quality of evidence (SoF Appendix 7)
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **MMC** Large [ ] Moderate [ ] Small [X] None [ ] **5-FU** Large Moderate Small None	**MMC vs placebo or no antimetabolite** *Increased risk of hypotony* *High risk:* RR 2.69 95% (CI) 0.74 to 9.85, 5 more per 100 (from 2 fewer to 13 more), ARI 5%, NNH 19 95% CI 60 fewer to 8 more. *Low risk:* RR 1.07, 95% (CI) 0.25 to 4.56, ARI 0% NNH 260 95% CI 10 fewer to 10 more. *Wound leak and shallow anterior chamber* No significant differences noted in these effects between groups using MMC and those using placebo. Variation in the rates of shallow anterior chamber may be influenced by heterogeneity in definitions as well as surgical technique. *Cataract formation* *High risk:* RR 1.38 95% (CI) 0.45 to 4.24, 2 more per 100 (from 7 fewer to 11 more, ARI 2%, NNH 45 95% CI 9 fewer to 14 more with MMC. *Low risk:* RR 1.93, 95% (CI) 0.98 to 3.8, 10 more per 100 (from 2 to 17 more), ARI 10%, NNH 10 95% CI 6 fewer to 57 more with MMC. *Overall:* RR 1.80, 95% CI: 1.00 to 3.22). 9 more per 100 (from 0 to 14 more), ARI 9%, NNH 11 with MMC **5-FU vs placebo or control** *Wound leak and shallow anterior chamber* *High risk:* No data available

	[ ] [ ] [X] [ ] **MMC vs 5-FU** Large [ ] Moderate [ ] Small [X] None [ ]	*Low risk* A 50% increase in wound leak (RR= 1.36, CI (1.00,1.84) and increased risk of anterior chamber shallowing (RR=1.99 CI(1.22,3.22)) heterogeneity reported) with the use of 5-FU. *These are temporary effects that are not very common in clinical practice.* *Epithelial toxicity & hypotonous maculopathy* Epithelial toxicity reported as slightly more common with 5-FU RR=1.23 CI (0.85,1.77) **MMC versus 5-FU** There is some evidence of less epitheliopathy (RR 0.23, 95% CI 0.11 to 0.47) and less hyphaema (RR 0.62, 95% CI 0.42 to 0.91) in the MMC group. Patients who received MMC reported more bleb leaks, wound leaks, late hypotony and cataracts compared to 5-FU (appendix 7). Quality of evidence was low as adverse outcomes were rare leading to imprecise estimates of effect.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** **MMC** Favours intervention [X] Favours control [ ] Intervention = Control *or* Uncertain [ ] **5-FU** Favours intervention [X] Favours control [ ] Intervention = Control *or* Uncertain [ ] ***Applicable to patients at low risk of surgical failure only as no data for patients at high risk of surgical failure.*** **MMC vs 5-FU** Favours intervention [ ] Favours control [ ] Uncertain [X]	**MMC vs placebo or no-antimetabolite** MMC results in fewer surgical failures and a reduction in IOP at 12 months compared to placebo or no–antimetabolite (moderate certainty evidence), with a small increase in the risk of hypotony. **(moderate magnitude of benefit)** **5-FU versus placebo or control** There is no data available for patients at high risk of surgical failure. For patients at low risk of surgical failure, 5-FU results in fewer surgical failures at 12 months compared to placebo or control (high certainty evidence) with a small increase in wound leak and anterior chamber shallowing. **(small magnitude of benefit)** **MMC versus 5-FU** In the subgroup of patients with intraoperative sponge application, MMC resulted in fewer surgical failures at 12 months compared to 5-FU (low certainty evidence). In the Cabourne SR, the side effect profile is reported for the overall patient cohort (intraoperative and postoperative use by any application method) with no subgroup analysis in patients treated with intraoperative sponge application. **(small magnitude of benefit)** **(small magnitude of harm)**
THERAPEUTIC INTERCHANGE	**Therapeutic alternatives available:**	No therapeutic alternatives available on the EML

FEASABILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	Both options are readily available in South Africa for other indications. MMC is already routinely used in clinical practice during trabeculectomy even though it is not listed on the EML. 5-FU has been used as an alternative to MMC during reported stock outs.
RESOURCE USE	**How large are the resource requirements?** **MMC** More intensive [X] Less intensive [ ] Uncertain [ ] **5-FU** More intensive [X] Less intensive [ ] Uncertain [ ] **MMC vs 5-FU** More intensive [ ] Less intensive [ ] Uncertain [ ]	**MMC** **Mitomycin 2mg** R249.75 per injection* **Mitomycin 10mg** R1092.73 per injection* Doses of mitomycin ranged from 0.1 to 0.5 mg/mL. Cost per application: R250 (assumes only 1 application obtained per 2mg vial). **5-FU** **Fluorouracil 50mg/mL injection (Floracor®):** R17.70 for a 5mL injection* R37.00 for a 10mL injection* Doses used: 25mg/mL or 50mg/mL Cost per application: R17.70 (assumes only 1 application obtained per vial) *Prices as per SEP database 20 July 2023 The resource requirements for trabeculectomy with adjunctive MMC or 5-FU will be greater compared to trabeculectomy without adjunctive therapy. While MMC and 5-FU are not listed on the EML for glaucoma management, anecdotal feedback suggests that it is already part of routine clinical practice. Inclusion on the EML is therefore unlikely to result in an incremental budget impact. Based on the current SEP, the cost per application with MMC is significantly more expensive compared to 5-FU. Utilizing an ARR 5%, (NNT 20 95% CI -89 to 9), the cost of treating 20 patients with intraoperative sponge application of MMC is R5000 to prevent 1 additional surgical failure that would result in a cost of R5500-7200 being averted for an Ahmed valve which is used in follow up surgery, as the current standard of care for patients with failed trabeculectomies. This excludes other surgical costs relating to re-operation.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	No reports of the participants' perception of their treatment for MMC (Wilkins M et al., 2005) or 5-FU (Green E et al., 2014). Both MMC and 5-FU are established in clinical practice and recognised as an option to reduce bleb failure in multiple international guidelines.
EQUITY	**Would there be an impact on health inequity?** Yes [X] No [ ] Uncertain [ ]	MMC is already routinely used during trabeculectomy even though it is not currently listed on the EML. Adding MMC to the EML will ensure access and reduce inequity.

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	31 Aug 2023	GT, ZA, MM	

REFERENCES:

American Academy of Ophthalmology: Preferred Practice Pattern Glaucoma Committee:. (2020, Nov). *Primary Open-Angle Glaucoma PPP 2020.* Retrieved from American Academy of Ophthalmology: https://www.aao.org/education/preferred-practice-pattern/primary-open-angle-glaucoma-ppp

Baboolal SO et al. (2018). South African Eye Study (SAES): ethnic differences in central corneal thickness and intraocular pressure. *Eye*, 749-756.

Burr J et al. (2012). Medical versus surgical interventions for open angle glaucoma. *Cochrane Database Syst Rev*.

Cabourne E, et al. (2015). Mitomycin C versus 5-Fluorouracil for wound healing in glaucoma surgery. *Cochrane Database Syst Rev.* .

Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert Committee; Canadian Ophthalmological Society. (2009). Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of glaucoma in the adult eye. *Can J Ophthalmol.*, S7-93.

Chan HL et al. (2017). Glaucoma surgery and induced stigmatism: a systematic review. *Eye and Vision*.

Cook, C. (2009). Glaucoma in Africa - Size of the Problem and Possible Solutions. *J Glaucoma*, 124-128.

De Fendi LI et al. (2013). Mitomycin C versus 5-fluorouracil as an adjunctive treatment for trabeculectomy: a meta-analysis of randomized clinical trials. *Clin Exp Ophthalmol.*, 798-806.

Esfandiari H et al. (2018). Treatment Outcomes of Mitomycin C-Augmented Trabeculectomy, Sub-Tenon Injection versus Soaked Sponges, after 3 Years of Follow-up. *Ophthalmology Glaucoma*, 66-74.

European Glaucoma Society. (2021). European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition. *British Journal of Ophthalmology*, 1-169.

Gillespie B et al. (2003). CIGTS Study group. History of intraocular pressure as a predictor of visual field progression in a randomized clinical trial of glaucoma treatment. *Controlled Clinical Trials*.

Green E et al. (2014). 5-Fluorouracil for glaucoma surgery. *Cochrane Database of Systematic Reviews*.

Gupta AV et al. (2022). Comparative evaluation of outcomes of novel approach of subconjunctival Mitomycin C (MMC) injection at the end of trabeculectomy versus intraTenon injection of MMC prior to the initial conjunctival incision – A pilot study. *Indian Journal of Ophthalmology*, 4194-4200.

Heijl a et al. (2002). Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Archives of Ophthalmology*, 1268-79.

Kapetanakis VV et al. (2016). Global variations and time trends in the prevalence of primary open angle . *Br J Ophthalmol*, 86-93.

Kass MA et al. (2002). The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Archives of Ophthalmology*, 701-13.

Kiuchi Y et al. (2023). Glaucoma Guideline Preparation Committee, Japan Glaucoma Society. The Japan Glaucoma Society guidelines for glaucoma 5th edition. *Jpn J Ophthalmol.*, 189-254.

Maier PC et al. (2005). Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ*, 331 .

Marais A et al. (2017). The medical management of glaucoma. *South African Family Practice*, 6-13.

Musch DC et al. (2009). Visual field progression in the Collaborative Initial Glaucoma Treatment Study the impact of treatment and other baseline factors. *Ophthalmology*, 200-7.

National Institute for Health and Care Excellence (NICE). (2022, Jan 26). *Glaucoma: diagnosis and management.* Retrieved from NICE: https://www.nice.org.uk/guidance/ng81

Pakravan M et al. (2017). Mitomycin C-augmented trabeculectomy: subtenon injection versus soaked sponges: a randomised clinical trial. *Br J Ophthalmol*, 1-6.

Robin AL et al. (1997). A long-term dose-response study of mitomycin in glaucoma filtration surgery. *Archives of Ophthalmology*, 969-74.

Salmon JF et al. (1993). The Prevalence of Primary Angle Closure Glaucoma and Open Angle Glaucoma in Mamre, Western Cape, South Africa. *(Arch Ophthalmol.*, 1263-1269.

Schellack N et al. (2017). Glaucoma: a brief update for 2017. *South African Family Practice*, 5-10.

Shaheer M et al. (2018). Comparison of Mean Corneal Endothelial Cell Loss after Trabeculectomy with and without Mitomycin C. *Journal of the College of Physicians and Surgeons Pakistan*, 301-303.

Shin DH et al. (1998). The role of adjunctive mitomycin C in secondary glaucoma triple procedure as compared to primary glaucoma triple procedure. *Ophthalmology*, 740-5.

STULTING, A. e. (2013). Glaucoma: The least the general practitioner should know. *Continuing Medical Education*, 159-163.

The Royal College of Ophthalmologists. (2022, June 24). *Management of Angle Closure Glaucoma Guideline.* Retrieved from The Royal College of Ophthalmologists: https://www.rcophth.ac.uk/resources-listing/management-of-angle-closure-glaucoma-guideline/

Wilkins M et al. (2005). Intra-operative mitomycin C for glaucoma surgery. *Cochrane Database Syst Rev.*

Appendix 1: Pubmed Search History for SRs

Search	Query	Results
#8	Search: **#5 OR #7** Filters: **Systematic Review**	28
#5	Search: **#1 AND #2** Filters: **Systematic Review**	11
#7	Search: **#1 AND #3** Filters: **Systematic Review**	26
#6	Search: **#1 AND #3**	1,894
#4	Search: **#1 AND #2**	718
#3	Search: **"mitomycin"[MeSH Terms] OR "mitomycin"[All Fields] OR "mitomycin c"[All Fields])**	21,539
#2	Search: **"fluorouracil"[All Fields] OR "fluorouracil"[MeSH Terms] OR fluorouracil[Text Word]**	65,323
#1	Search: **(("glaucoma"[MeSH Terms] OR "glaucoma"[All Fields] OR "glaucomas"[All Fields]) AND ("surgery"[MeSH Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields] OR "surgery s"[All Fields] OR "surgerys"[All Fields] OR "surgeries"[All Fields]))**	29,133
#0	Search: **Clipboard**	28

Pubmed Search History for RCTs for Mitomycin C and 5-Fluorouracil

Search	Query	Results
#6	Search: **fluorouracil AND glaucoma** Filters: **Randomized Controlled Trial, from 2013/7/1 - 2023/8/8**	12
#5	Search: **fluorouracil AND glaucoma** Filters: **Randomized Controlled Trial**	83
#4	Search: **fluorouracil AND glaucoma**	772
#3	Search: **mitomycin AND glaucoma** Filters: **Randomized Controlled Trial, from 2010/1/1 - 2023/8/8**	97
#2	Search: **mitomycin AND glaucoma** Filters: **Randomized Controlled Trial**	200
#1	Search: **mitomycin AND glaucoma**	1,987
#0	Search: **Clipboard**	97

Appendix 2: Summary of Findings Table (Wilkins M et al., 2005)

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Intraoperative Mitomycin C compared with no antimetabolite or placebo for trabeculectomy surgery for glaucoma

Patient or population: People undergoing trabeculectomy surgery with glaucoma

Settings: Eye clinics and hospitals

Intervention: Intraoperative Mitomycin C applied in any dose for any duration

Comparison: Placebo application or nothing

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	control	mitomycin C				
Trabeculectomy failure at 12 months	**Low risk population**		RR 0.37 (0.26 to 0.51)	698 (11)	+++O moderate	medium risk population poorly designed studies may underestimate effect
	280 per 1000	77 per 1000 ([value] to [value])				
	Medium risk population					
	127 per 1000	135 per 1000 ([value] to [value])				
	High risk population					
	505 per 1000	156 per 1000 ([value] to [value])				
mean intraocular pressure mmHg at 12 months	The mean IOP ranged across control groups from 15.9 to 23.9 mmHg	The mean IOP in the intervention groups was 11.1 to 14.6 mmHg	the WMD was -4.1 mmHg [-4.68 to -3.34] mmHg	380 [8]	+++O moderate	

complications wound leak by 12 months	**Low risk population**		RR 1.84 (0.72 to 4.66)	333 (7)	++OO low	no events reported in trials of high risk patients
	45 per 1000	114 per 1000 ([value] to [value])				
	Medium risk population					
	84 per 1000	112 per 1000 ([value] to [value])				
	High risk population					
	inestimable	inestimable				
complications hypotony occurring up to 12 months	**Low risk population**		RR 1.8 (0.79 to 4.12)	488 (10)	++OO low	inconsistently defined and reported
	58 per 1000	61 per 1000 ([value] to [value])				
	Medium risk population					
	14 per 1000	37 per 1000 ([value] to [value])				
	High risk population					
	31 per 1000	83 per 1000 ([value] to [value])				
complications shallow anterior chamber occurring within 12 months	**Low risk population**		RR 1.14 (0.42 to 3.07)	441 (10)	++OO low	inconsistently defined and reported
	169 per 1000	151 per 1000 ([value] to [value])				
	Medium risk population					
	0 per 1000	9 per 1000 ([value] to [value])				
	High risk population					
	145 per 1000	200 per 1000 ([value] to [value])				

cataract formation by 12 months	**Low risk population**		RR 1.8 (1.00 to 3.22)	482 (7)	+++O moderate	outcome not relevant to medium risk population because these are combined cataract extraction and glaucoma procedures
	93 per 1000	190 per 1000 ([value] to [value])				
	High risk population					
	57 per 1000	80 per 1000 ([value] to [value])				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk Ratio; [other abbreviations, e.g.. OR, etc]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Appendix 3: Summary of Findings Table (Green E et al., 2014)

Summary of findings 6. Intraoperative 5-Fluorouracil versus placebo or control for glaucoma surgery

Intraoperative 5-FU versus placebo or control for glaucoma surgery

Patient or population: participants with glaucoma surgery
Settings:
Intervention: intraoperative 5-FU versus placebo or control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Peroperative 5-FU versus placebo or control				
Failure at 12 months Need for repeat surgery or uncontrolled IOP (usually more than 22 mm Hg) despite additional topical or systemic medications	**267 per 1000**	**182 per 1000** (136 to 246)	**RR 0.68** (0.51 to 0.92)	711 (4 studies)	⊕⊕⊕⊕ **high**	-
Mean intraocular pressure at 12 months	The mean intraocular pressure at 12 months in the control groups was **14.89 mm Hg**	The mean intraocular pressure at 12 months in the intervention groups was **1.04 lower** (1.65 to 0.43 lower)	-	711 (4 studies)	⊕⊕⊕⊕ **high**	-
Complications - wound leak Follow-up: 12 months	**156 per 1000**	**212 per 1000** (156 to 287)	**RR 1.36** (1 to 1.84)	711 (4 studies)	⊕⊕⊕⊕ **high**	-
Complications - hypotonous maculopathy Follow-up: 12 months	**11 per 1000**	**17 per 1000** (5 to 58)	**RR 1.47** (0.42 to 5.12)	711 (4 studies)	⊕⊕⊕⊖ **moderate**	-
Complications - shallow anterior chamber Follow-up: 12 months	**61 per 1000**	**122 per 1000** (75 to 197)	**RR 1.99** (1.22 to 3.22)	711 (4 studies)	⊕⊕⊕⊕ **high**	-
Complications - epithelial toxicity Follow-up: 12 months	**103 per 1000**	**127 per 1000** (88 to 182)	**RR 1.23** (0.85 to 1.77)	711 (4 studies)	⊕⊕⊕⊖ **moderate** [1]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
5-FU: 5-Fluorouracil; **CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The broad confidence interval spans both a clinically advantageous and disadvantageous outcome. Consequently, the quality of evidence is reduced.

Appendix 4: Summary of the SR by (Cabourne E, et al., 2015): Head to head comparison

(Cabourne E, et al., 2015) **Mitomycin C versus 5-Fluoruracil for wound healing in glaucoma surgery**.

This SR included 11 RCTS with a total of 679 participants that were were grouped into 3 categories as detailed below and slightly different to those reported in the reviews by (Wilkins M et al., 2005) and (Green E et al., 2014):

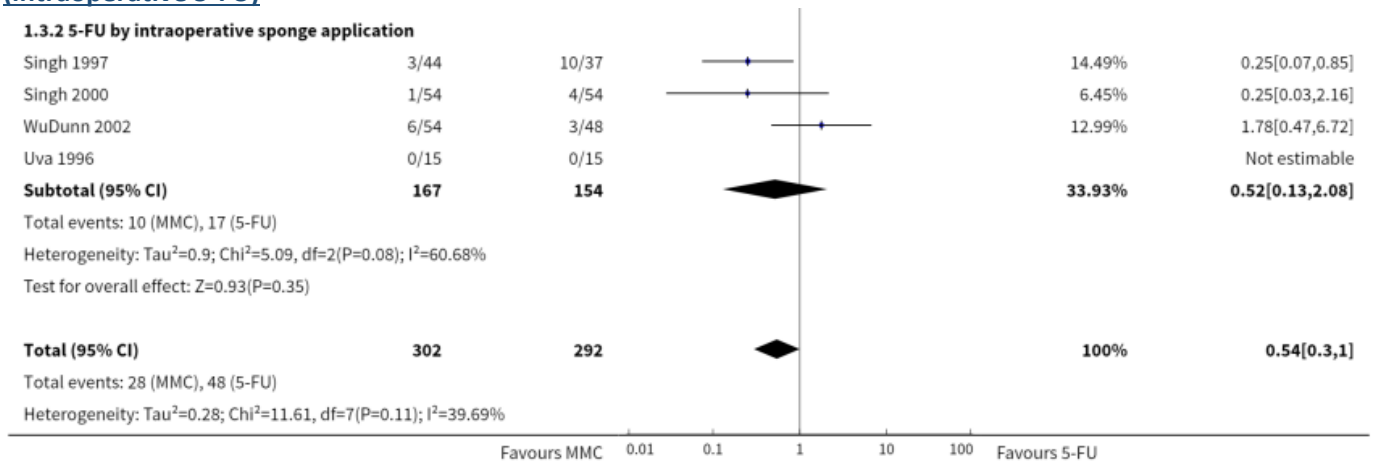
- High risk of trabeculectomy failure: people with previous glaucoma or extracapsular cataract surgery, people of African origin and people with secondary glaucoma or congenital glaucoma
- Medium risk of trabeculectomy failure: (combined surgery) people undergoing trabeculectomy with extracapsular cataract surgery
- Low risk of trabeculectomy failure: (primary trabeculectomy) people who have received no previous surgical eye intervention. People who underwent previous laser procedures could be included in this group.

Four interventions were considered:

- Use of intraoperative MMC versus intraoperative 5-FU,
- Use of intraoperative MMC versus post-operative 5-FU,
- Use of intraoperative MMC versus Intraoperative and postoperative 5-FU
- Use of intraoperative and postoperative MMC versus intraoperative 5-FU and post-operative 5-FU.

Results of the use of intraoperative MMC versus intraoperative 5-FU:

Figure 6: Outcome 3 – failure of functioning trabeculectomy at one year depending on 5-FU administration technique (intraoperative 5-FU)



Study	MMC	5-FU
Singh 1997 High risk of trabeculectomy failure	(44 eyes) Intraoperative sponge application Dose: 0.5mg/mL for 3.5 min Location: between scleral flap and conjunctiva	(37 eyes) Intraoperative sponge application Dose: 50mg/mL for 5 min Location: between scleral flap and conjunctiva
Singh 2000 Low risk of trabeculectomy failure	(54 eyes) Intraoperative sponge application Dose: 0.4mg/mL for 2 min Location: not stated	(54 eyes) Intraoperative sponge application Dose: 50mg/mL for 5 min Location: not stated
Wa Dunn 2002 Low risk of trabeculectomy failure	(58 eyes) Intraoperative sponge application Dose: 0.2mg/mL for 2 min Location: not stated	(57 eyes) Intraoperative sponge application Dose: 50mg/mL for 5 min Location: not stated
Uva 1996 Low risk of trabeculectomy failure	(15 eyes) Intraoperative sponge application Dose: 0.2mg/mL for 2 min Location: between sclera and Tenon's capsule	(15 eyes) Intraoperative sponge application Dose: 50mg/mL for 5 min Location: between sclera and Tenon's capsule

Appendix 5: Comparison in the types of participants as defined in the 3 SRs included in this review

	MMC (Wilkins M et al., 2005)	5-FU (Green E et al., 2014)	MMC v 5-FU (Cabourne E, et al., 2015)
High risk of failure	People who have had previous glaucoma drainage surgery or previous surgery involving anything more than trivial conjunctival incision, including cataract surgery; people with one or more of the following forms of glaucoma: glaucoma secondary to intraocular inflammation, congenital glaucoma and neovascular glaucoma	People who have had previous glaucoma drainage surgery or surgery involving anything more than trivial conjunctival incision including cataract surgery, glaucoma secondary to intraocular inflammation, congenital glaucoma and neovascular glaucoma	People with previous glaucoma or extracapsular cataract surgery, **people of African origin** and people with secondary glaucoma or congenital glaucoma.
Trabeculectomy combined with cataract surgery *(outside of PICO)*	People undergoing trabeculectomy with extra-capsular cataract extraction and intraocular lens implant	People undergoing trabeculectomy with extracapsular cataract extraction and intraocular lens implant;	People undergoing trabeculectomy with extra-capsular cataract surgery
Primary trabeculectomy	People who have received no previous surgical intervention as defined above. This group may include people who have had previous medical therapy, laser procedures or both.	People who have received no previous surgical intervention as defined above. This group may include people who have had previous laser procedures.	People who have received no previous surgical intervention. People who have had previous laser procedures may be included in this goup.

Appendix 6: MMC versus 5-FU – Comparison of adverse effects

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8 Postoperative Complications	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Bleb leak	2	154	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.32, 4.68]
8.2 Wound leak	6	391	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.51, 2.71]
8.3 Late hypotony	4	211	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.41, 4.63]
8.4 Maculopathy	4	342	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.35, 8.33]
8.5 Cataract	4	275	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.65, 4.61]
8.6 Shallow anterior chamber	5	311	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.67, 2.21]
8.7 Choroidal detachment	8	494	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.45, 1.63]
8.8 Epitheliopathy	8	419	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.11, 0.47]
8.9 Tenon cyst	3	177	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.20, 4.38]
8.10 Hyphaema	4	250	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.42, 0.91]
8.11 Suprachoroidal haemor-rhage	3	303	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.09, 5.66]
8.12 Endophthalmitis	4	315	Risk Ratio (M-H, Random, 95% CI)	3.89 [0.44, 34.57]

Appendix 7: SUMMARY OF FINDINGS – MMC versus 5-FU

Summary of findings for the main comparison. MMC compared to 5-FU for wound healing in glaucoma surgery

MMC compared to 5-FU for wound healing in glaucoma surgery

Patient or population: wound healing in glaucoma surgery
Settings:
Intervention: MMC
Comparison: 5-FU

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants/eyes (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	5-FU	MMC				
Failure of functioning trabeculectomy at 1 year	**Study population**		Low-risk population RR 0.65 (95% CI 0.19 to 2.20) High-risk population RR 0.49 (95% CI 0.22 to 1.08)	634 (11 RCTs: 6 including low-risk population and 5 including high-risk population)	⊕⊕⊙⊙ LOW [1,2]	
	Low-risk population: 74 per 1000 High-risk population: 272 per 1000	Low-risk population: 50 per 1000 High-risk population: 137 per 1000				
Intraocular pressure at 1 year	The mean intraocular pressure at 1 year ranged across 5-FU groups. Low-risk population: 10.9 to 14.3 mmHg High-risk population: 14.8 to 16.3 mmHg	The mean intraocular pressure at 1 year in the MMC groups had a range of values. Low-risk population: 9.9 to 11.6 mmHg High-risk population: 8.6 to 13.7 mmHg	-	386 (7 RCTs: 3 including low-risk population and 4 including high-risk population)	⊕⊕⊙⊙ LOW [1,3]	
Loss of 2 or more lines of Snellen visual acuity at 1 year	**Study population**		Low-risk population RR 2.00 (95% CI 0.53 to 7.59) High-risk population RR 0.81 (95% CI 0.36 to 1.80)	328 (5 RCTs: 2 including low-risk population and 3 including high-risk population)	⊕⊕⊙⊙ LOW [2,4]	
	Low-risk population: 47 per 1000 High-risk population: 115 per 1000	Low-risk population: 94 per 1000 High-risk population: 96 per 1000				
	Study population		RR 1.37 (95% CI 0.41 to 4.63)	211 (4 RCTs)	⊕⊕⊙⊙ LOW [2,4]	
Postoperative complications: late hypotony	37 per 1000	59 per 1000				
Postoperative complications: choroidal detachment	**Study population**		RR 0.86 (95% CI 0.45 to 1.63)	494 (8 RCTs)	⊕⊕⊙⊙ LOW [1,2]	
	68 per 1000	70 per 1000				
Postoperative complications: endophthalmitis	**Study population**		RR 3.89 (95% CI 0.44 to 34.57)	315 (4 RCTs)	⊕⊕⊙⊙ LOW [1,2]	
	0 per 1000	19 per 1000				
Quality of life at 1 year						Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
5-FU: 5-Fluorouracil; **CI:** confidence interval; **MMC:** mitomycin C; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for risk of bias: only one study at low risk of bias in all domains
[2]Downgraded for imprecision: wide confidence intervals
[3]Downgraded for inconsistency: $I^2 = 60\%$
[4]Downgraded for risk of bias: no study at low risk of bias in all domains