South African National Essential Medicine List
Adult Hospital Medication Review Process
Component: Eye conditions

MEDICINE REVIEW

1. Executive Summary

Date: 9 February 2023
Medicine (INN): Hyaluronidase
Medicine (ATC): B06AA03
Indication (ICD10 code): Cataract surgery H26.0-4/H26.8-9/H59.0
Patient population: Adult patients
Prevalence of condition: The prevalence of cataract surgery in South African is not known. However, an estimated 60 000 cataract surgeries were reportedly performed in the public sector for the period April 2019 to March 2020 *(Source: NDoH, DHIS data on file).*
Level of Care: Adult Hospital Level (regional and district level of care)
Prescriber Level: Specialist consultation
Motivator/reviewer name(s): G Thom, T Kredo, T Leong, N Gloeck, M Mthethwa
PTC affiliation: GT - KZN Provincial PTC

Key findings

- We conducted a review of clinical practice guidelines (CPGs), systematic reviews of randomised controlled trials (RCTs) and RCTs.
- One systematic review, two RCTs and one CPG were identified that included comparisons of interest
- NICE CPG (2017) was assessed as high quality using AGREE II tool. Recommendations include consideration of hyaluronidase as an adjunct to sub-Tenon's anaesthesia, particularly if trying to stop the eye moving during surgery (akinesia); low certainty evidence, conditional recommendation.
- The systematic review reported on intraoperative pain, surgical (surgeon) satisfaction and patient satisfaction.
- The effect of hyaluronidase on intraoperative pain during eye surgery is uncertain.
- Moderate quality evidence showed improved patient satisfaction scores (2 RCTs; n=122, p<0.05) with the use of hyaluronidase. Each study had assessed satisfaction using a different method, and therefore no meta-analysis was conducted.
- Studies assessing surgical satisfaction could not be meta-analysed as outcome measures were heterogeneous. Moderate quality evidence shows improved surgical satisfaction scores in 2 RCTs (n=144, p=0.02 and p<0.001) with the use of hyaluronidase, but no difference in another study (1 RCT; n= 20, p=0.96).
- No harms were reported in the studies associated with anaesthesia solution with or without hyaluronidase.
- The use of hyaluronidase to improve akinesia during surgery is supported by the NICE CPG (2017) and Rowley 2000, but available evidence is conflicting, and use may be determined by surgeon preference.

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 a conditional recommendation for the use of hyaluronidase as an adjunct to anaesthesia for peri-orbital block. Its potential for improved akinesia may be beneficial in certain clinical settings, (extracapsular cataract surgery or manual small incision cataract surgery is still the predominant method used at many

sites locally). As the technique uses larger incisions and it is difficult to stabilize the eye with one instrument, movement of the eye increases the risk of posterior capsule rupture with vitreous loss resulting in poor visual outcomes. **Rationale:** Operating with good akinesia is of utmost importance for trainee and inexperienced surgeons performing extracapsular surgery which is of lesser importance when phacoemulsification is used with smaller incisions and two hands available to stabilize the eye. Hyaluronidase also assists with spreading fluid in the tissues, which reduces the risk of elevated intraocular pressure. A high coincidence rate exists between sharp rise of IOP and undesirable intraoperative complications such as: shallowing of anterior chamber, herniation of iris through incision site and stromal corneal oedema. Javrishvili (2021)). **Level of Evidence: Low quality evidence** **Review indicator:**
NEMLC RECOMMENDATION (MEETING OF 23 FEBRUARY 2023): NEMLC supports the recommendation of the Expert Review Committee as detailed above.
Monitoring and evaluation considerations
Research priorities

2. **Name of author(s)/motivator(s):** G Thom, T Leong, N Gloeck, T Kredo, M Mthethwa

3. **Author affiliation and conflict of interest details**

   GT (KwaZulu-Natal Department of Health), TK (Cochrane South Africa, South African Medical Research Council (SAMRC), Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, co-director of the South African GRADE Network), TL, NG and MM (Cochrane South Africa, South African Medical Research Council (SAMRC) have no interests related to hyaluronidase.

   TK, TL, NG and MM are partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies).

4. **Introduction/ Background**

   Hyaluronidase is an endoglycosidase enzyme that breaks down hyaluronic acid in the extracellular matrix (Jung 2020). In clinical practice, this agent has routinely been administered with local anaesthetic injection to improve the rate of onset of analgesia and akinesia (Rüschen 2018, Atkinson, 1949). Optimal anaesthetic blocks in ophthalmologic surgery require adequate spread of local anaesthetic through the orbital cavity. However, connective tissue membranes impede distribution of local anaesthetic which may be addressed with the adjunctive administration of hyaluronidase (Rüschen 2018, Koornneef 1988, Buhren 2016). Hyaluronidase in local anaesthetic fluid also appears to prevent increases in intraocular pressure during surgery (Rüschen 2018, Dempsey 1997). Furthermore, expert opinion is that hyaluronidase allows smaller volumes of local anaesthesia to be used. In South Africa, a large proportion of eye surgery is performed by medical officers and non-specialist cataract surgeons often in district hospitals with the background of pressure on surgical outputs due to a large unmet burden of preventable blindness due to cataracts. For these clinicians optimal blocks are essential for good surgical outcomes. Akinesia associated with hyaluronidase, is thus considered an important outcome by most of the local ophthalmologists. However, the available evidence is uncertain with conflicting results.

   An evidence review is being undertaken which will inform the decision of whether to include or exclude hyaluronidase on the Adult Hospital Level Essential Medicine List. Hyaluronidase is being considered as an adjunct to local anaesthesia to improve the quality of anaesthesia and analgesia in cataract surgery.

5. Purpose/Objective i.e., PICO

Population	Adult patients (≥18) undergoing peri-ocular blocks for eye surgery
Intervention	Hyaluronidase co-administered with local anaesthetic agent(s)
Control	Placebo or local anaesthesia only (lidocaine, bupivacaine)
Outcomes	Akinesia during surgery Intraoperative pain Adverse outcomes (surgical complications) Patient satisfaction Surgeon satisfaction
Study designs	Systematic reviews of RCTs or RCTs. Observational studies will only be sourced if the latter are unavailable.

6. Methods:

a. Data sources:
Clinical Practice Guidelines sources searched were the Guidelines International Network (GIN) Library and the National Institute for Health and Care Excellence (NICE). Systematic reviews and randomised controlled trials were sought in PubMed and Epistemonikos. To identify planned and ongoing studies, WHO's International Clinicals Trials Registry Platform (ICTRP) as well as ClinicalTrials.gov were searched.

b. Search strategy – A search strategy was developed for PubMed and Epistemonikos (Appendix 1).

c. **Screening, data extraction and analysis, evidence synthesis:** Records were retrieved (MM and TL) and screened independently and in duplicate (GT and TL). Thereafter, full text screening was done by two reviewers (GT and TL). Any discrepancies were discussed with TK. We screened for systematic reviews, followed by screening for any additional RCTs that were not included in the eligible systematic review(s). Data extraction for systematic reviews and RCTs was done by one reviewer and checked by a second reviewer. Eligible clinical guidelines were appraised by two reviewers (GT and NG) using the AGREE II tool; systematic reviews with the AMSTAR II Checklist (GT and NG), and RCTs assessed for Risk of Bias using the Cochrane's RoB 2.0 Tool. Data were extracted into Characteristics of Included studies tables (tables 2 and 3). For dichotomous outcomes, we reported risk ratios (RR) with 95% confidence intervals (CI) and results from the review or trial where possible. Where available, we reported on the GRADE (level of certainty) of the evidence, considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness.

Excluded studies: Reasons for excluding full-texts were agreed in duplicate (GT and TL) with a third reviewer (TK) resolving any disputes, as required.

7. Results

We searched PUBMED and Epistemonikos on 12 August 2022 and retrieved 20 records for screening. One duplicate record was excluded and another that was not available in English. Sixteen records were excluded for having the incorrect population, comparator and/or intervention and study design, after full-text assessment. One systematic review and one RCT were considered for evidence synthesis. There were no ongoing trials identified. See appendix 2 for the PRISMA flow diagram, appendix 3 for characteristics of included studies and appendix 4 for list of excluded studies and the rationale for exclusion.

a. Guidelines

We identified one guideline, a NICE Guideline: Cataracts in adults: management, 2017 (NICE, 2017). This guideline was assessed using the AGREE II tool as good quality and suggests hyaluronidase as an adjunct to sub-Tenon's anaesthesia, particularly for akinesia (see table below and appendix 5).

Guideline citation and website	Recommendation	Appraisal AGREE II
NICE 2017 Cataracts in Adults: management: https://www.nice.org.uk/guidance/ng77	Consider hyaluronidase as an adjunct to sub-Tenon's anaesthesia, particularly if trying to stop the eye moving during surgery (akinesia); *low certainty evidence, conditional recommendation* Trade off between benefits and harms: "…evidence showed lower levels of anaesthetic were necessary to achieve a sub-Tenon's block when hyaluronidase was added, but noted this did not represent the volume of anaesthetic necessary for adequate pain control, but rather the volume necessary to achieve eye akinesia (an outcome which some surgeons may consider highly desirable, but one which others may not be particularly concerned with)." Secondary Comment: Low-quality evidence from 1 RCT of 62 participants showed that those who received anaesthesia with hyaluronidase had a 2.4-fold reduction in median effective local anaesthetic volume needed to achieve a sub-Tenon's block. 1 study showed that a high average volume (6.4mL) of anaesthetic was needed in people randomised not to receive hyaluronidase. The injection of this volume into the sub-Tenon's space could elevate the risk of vitreal compression.	Overall assessment 92% See appendix 5.

Table 1: AGREE 2 assessment of the 2017 NICE Clinical Guideline on cataract management in adults

b. **Systematic review and randomised controlled trials**

Description of included studies:
One systematic review (Rüschen 2018) and one RCT (Swathi 2020) was eligible for review. In addition, a RCT (Rowley 2000) included in the systematic review but that was not reviewed for akinesia (as authors considered this not to be relevant for most cataract surgeries) has been reviewed.

- ***Systematic review:***
  Rüschen 2018: One systematic review of seven RCTs (of 500 study participants, 18 years or older presenting for ophthalmic surgery) was identified (Rüschen 2018) to determine if hyaluronidase as an adjuvant to local anaesthetic solutions reduced intraoperative pain. The primary outcome was intraoperative pain as measured by analogue rating scales. Secondary outcome measures included incidence of harm (reported as a narrative); participant and surgical satisfaction, as documented by scoring systems, and economic outcomes or cost calculations (reported as a narrative). See the characteristics of included studies table in appendix 3 for details.

  Akinesia was not reported as the authors stated that, due to most modern surgical techniques, the majority of surgeons could carry out most operations without depending on fully established akinesia (except in difficult operations or training situations where profound akinesia is necessary). However, as the NICE guideline (2017) recommends hyaluronidase as an adjunct to sub-Tenon's anaesthesia, particularly for akinesia, the RCT by Rowley et al (2000) that reports on akinesia and was included in the systematic review will be reviewed (see appendix 4).

The systematic review was assessed as high quality using the AMSTAR 2 tool (see table 2 and appendix 6). However, according to GRADE, the quality of the reviewed RCTs for intraoperative pain was assessed as low quality (due to imprecision and inconsistency, lack of data and small sample size); and for patient and surgical satisfaction as moderate quality (downgraded due to imprecision secondary to small sample size).

Systematic review	Recommendation	Appraisal AMSTAR 2
Rüschen H, et al. Use of hyaluronidase as an adjunct to local anaesthetic eye blocks to reduce intraoperative pain in adults. Cochrane Database Syst Rev. 2018 Mar 2;3(3):CD010368.	The effects of adding hyaluronidase to local anaesthetic fluid on pain outcomes in people undergoing eye surgery are uncertain due to the low quality of evidence available. A well designed RCT is required to address inconsistency and imprecision among the studies and to determine the benefit of hyaluronidase to improve analgesia during eye surgery. Participant and surgical satisfaction is higher with hyaluronidase compared to the control groups, as demonstrated in moderate quality studies.	High Quality Review. See appendix 6

Table 2: AMSTAR 2 assessment of the systematic review by Rüschen et al (2018)

- ***Randomised controlled trials:***

  Swathi et al (2020): This single eligible RCT selected for review, was conducted in a single hospital in India, where adult patients (n=202) presented with uncomplicated cataracts, over a period of 15-months. Patients were scheduled for Manual Small Incision Cataract, and randomly assigned to either a control group (n=100), administered local anaesthesia without hyaluronidase, or a treatment group (n=102), administered adjuvant hyaluronidase, dosed at 50IU/ml. The aim of this study was to determine whether hyaluronidase was necessary as an anaesthetic adjuvant for peribulbar anaesthesia during cataract surgery and to assess differences in anaesthetic outcomes (extra ocular movements, ease of procedures and orbicularis oculi action) utilising a surgeon score card. Post operatively, the patient was given a visual analogue scale (0–10) to grade the perceived pain at the beginning and end of surgery.

  Rowley et al (2000):
  This RCT was summarised as it was included in both the systematic review by Rüschen et al (2018) and the NICE CPG (2017) and reported specifically on akinesia which was not reported in the systematic review. The study was conducted in a single hospital in the United Kingdom on 150 patients scheduled for elective cataract surgery. Patients were randomly assigned to a control group (n=74) who had routine local anaesthesia administration and a treatment group (n=76) who had 30IU/ml hyaluronidase added to the anaesthetic solution. The aim of this study was to determine the effect of hyaluronidase on the quality of the local anaesthesia blocks, assessing akinesia and eyelid movements. The degree of akinesia was measured using a four-point scale: 0 = complete movement remaining, 1 = moderate movement, 2 = slight movement (<3 mm in any direction), 3 = no movement). Eyelid movement was assessed using a three-point scale: (0 = normal movement, 1 = reduced movement, 2 = absent movement).
  Pain was assessed intraoperatively, immediately after injection and perioperatively, immediately after surgery, using a 10-point visual analogue scale (0 being no pain, 10 excruciating pain).

Effectiveness of hyaluronidase *vs*. no hyaluronidase

- **Pain**

  - **Intraoperative pain** (Rüschen 2018)
    The effect of hyaluronidase on intraoperative pain is uncertain.

    Dichotomous data: (4 RCTs, n=289)
    - 0.25% (25/1000) vs 0.30% (301/1000); RR 0.83 (95% CI 0.48 to 1.42); I^2=41, low certainty evidence due to imprecision and inconsistency.

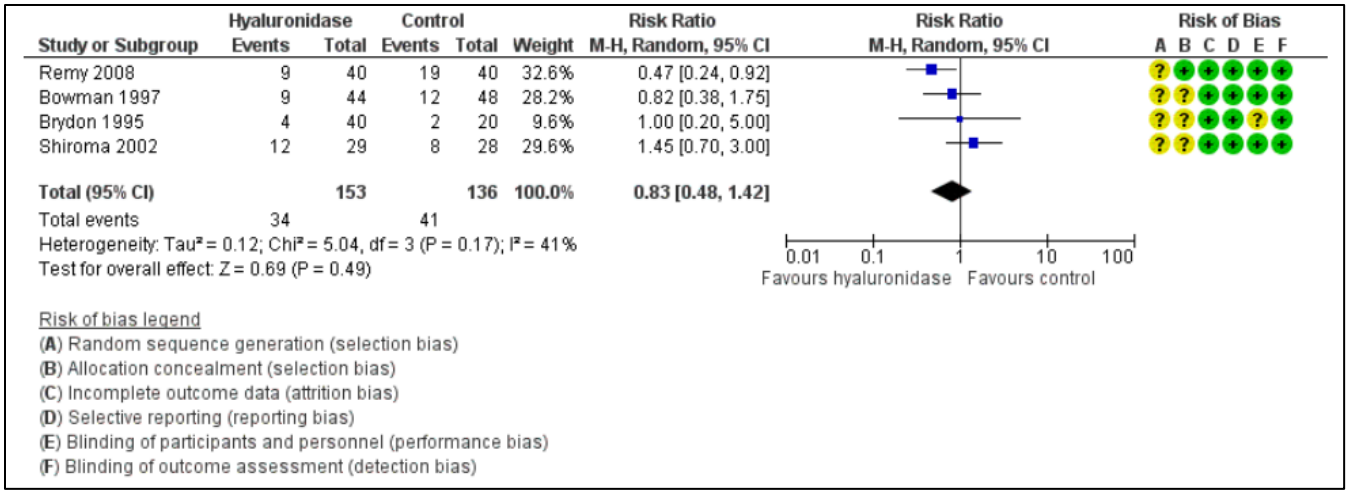

Figure 2: Forest plot of hyaluronidase versus control for intraoperative pain (dichotomous data as measured by analogue rating scales)

Continuous data: (3 RCTs, n=211)

- Study data could not be meta-analysed as outcome measures were not consistent. Khandwala et al (2008) and Rowley et al (2000) did not report standard deviations (SDs). We are uncertain of the effect of hyaluronidase on intraoperative pain in these groups. Sedghipour et al (n=42) suggested there may be a reduction in intraoperative pain. Quality of evidence was low due to imprecision and inconsistency in measurement, lack of data and small sample size.

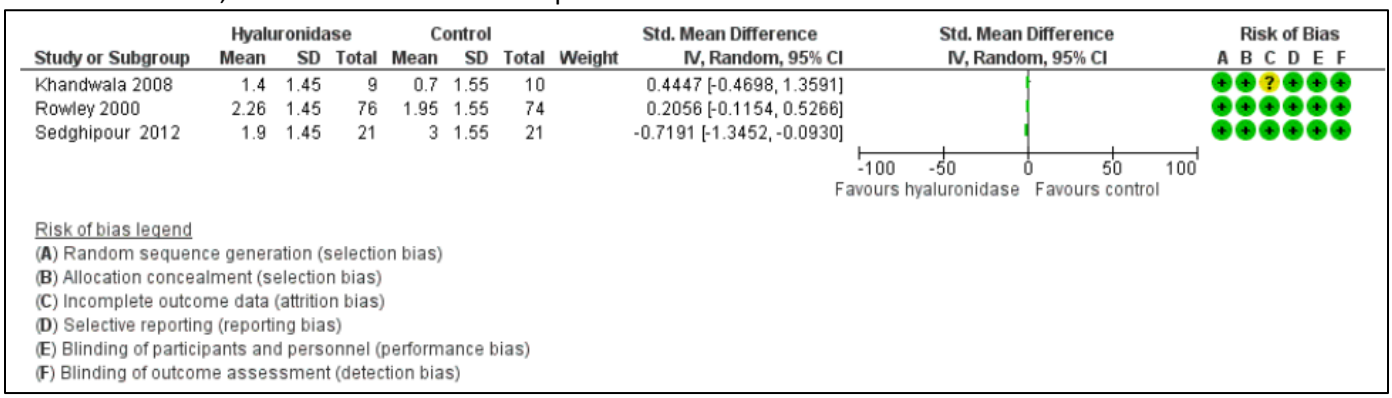

Figure 3: Forest plot of hyaluronidase versus control for intraoperative pain (continuous data as measured by analogue rating scales)

- **Patient pain score** (Swathi 2020): Prior to surgery, eight patients in the treatment group vs seven in the control group reported a pain score of 6 or more (p=0.44). After surgery, no patients in the treatment group vs one in the control group scored 6 or more (p=0.093).

- **Post injection pain score** (Rowley 2000): Treatment group 2.26 versus control group 1.95, p value reported as not significant.

- **Post operative pain score** (Rowley 2000): Treatment group 1.04 versus control group 1.03, p value reported as not significant.

- **Participant satisfaction** (Rüschen 2018)
  - Hyaluronidase treatment group had significantly higher participant satisfaction scores (Two RCTs; n=122, p<0.05; moderate certainty evidence due to imprecision secondary to small sample size).

Hyaluronidase increased participant satisfaction scores.

- **Surgical satisfaction** (Rüschen 2018)
  - Hyaluronidase showed superior surgical satisfaction compared to control in two RCTs; n=121 (Remy 2008, p<0.001; Sedghipour 2012, p=0.02), but no difference in one small RCT of 20 participants, p=0.96 (Khandwala 2008); moderate certainty evidence due to imprecision secondary to small sample size.

  Hyaluronidase increased surgical satisfaction scores.

- **Incidence of harm**
  - *Rüschen 2018:* No reported harm due to the addition of hyaluronidase in any of the studies.
  - *Swathi 2020:* Intraoperative complications were not attributed to the anaesthetic solution (with or without hyaluronidase).
  - *Rowley 2000:* Surgical complications were not associated with anaesthetic block (with or without hyaluronidase).

- **Akinesia and analgesia**

  Swathi 2020:
  - **Time for onset to akinesia:** Treatment group: 1.5–5 min (mean 2.3±SD 0.6; 95% CI 2.2–2.4 min) *vs*. Control: 1.5–5.5 min (mean 2.5±SD 0.7; 95% CI: 2.4–2.6 min); p=0.004.
  - **Time for onset to analgesia:** Treatment group: 1.4–3.5 min (mean 2.2±SD 0.4; 95% CI: 2.1–2.2 min) vs. Control: 1.5–4.25 min (mean 2.3±SD 0.5; 95% CI: 2.2–2.4 min); p=0.005.
  - ~~o~~ **Anaesthetic augmentation:** Five patients in the treatment group compared to nine patients in the control group required augmentation of the anaesthetic block (p=0.3).
  - **Extra ocular movements:** Nine patients in the treatment group vs 11 patients in the control group had unsatisfactory akinesia, graded as moderate movements or more by the operating surgeon (one patient in the control group had no restriction of movements despite repeat peribulbar anaesthesia, but due to adequate analgesia and patient co-operation, the surgery was completed). There was no difference in surgeon scoring of akinesia, comfort/ease during surgery and orbicularis oculi action.

  A faster onset of akinesia and analgesia was observed with the use of hyaluronidase (as an adjuvant), but the difference is clinically negligible, as the mean difference between the two groups was less than 30 seconds.

  Rowley 2000:
  - **Akinesia score (10 minutes after performance of block):** Treatment group 2.32 vs control group 1.43. (p<0.01)
  - **Akinesia:** Complete akinesia was achieved in 40 cases in the treatment group compared to 10 cases in the control group (p value not provided).

  Adjunctive hyaluronidase resulted in quicker onset of akinesia and greater rate of akinesia, but the absolute effect may not be clinically significant.

8. **Alternative agents:** Not applicable

9. **Conclusion:** There is uncertainty regarding the use of adjuvant hyaluronidase to local anaesthetic solution to reduce pain during eye surgery due to the low quality of the available evidence. Moderate quality evidence shows improved patient and surgical satisfaction scores with the use of hyaluronidase. Use of hyaluronidase to improve akinesia during surgery is supported by the NICE guideline and Rowley 2000, but available evidence is conflicting and use may be determined by surgeon preference.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** • **Analgesia** High: ☐ Moderate: ☐ Low: ☒ Very low: ☐ • **Surgical satisfaction** High: ☐ Moderate: ☒ Low: ☐ Very low: ☐ • **Patient satisfaction** High: ☐ Moderate: ☒ Low: ☐ Very low: ☐ • **Akinesia** High: ☐ Moderate: ☒ Low: ☐ 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	• **Analgesia** Low quality evidence due to marked heterogeneity, imprecision and inconsistency, lack of data and small sample size. • **Surgical satisfaction** Moderate quality evidence due to imprecision secondary to small sample size. • **Patient satisfaction** Moderate quality evidence due to imprecision secondary to small sample size. • **Akinesia** Moderate quality evidence due to imprecision secondary to small sample size.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** • **Analgesia** Large: ☐ Moderate: ☐ Small: ☐ None: ☒ • **Patient satisfaction** Large: ☐ Moderate: ☒ Small: ☐ None: ☐ • **Surgical satisfaction** Large: ☐ Moderate: ☒ Small: ☐ None: ☐ • **Akinesia** Large: ☐ Moderate: ☒ Small: ☐ None: ☐	• **Analgesia** *Dichotomous scores:* RR 0.83 (0.48 to 1.42) *Continuous scores:* Uncertain • **Patient satisfaction** Improved patient satisfaction scores with the use of hyaluronidase (2 RCTs; n=122, p<0.05) • **Surgical satisfaction** Improved satisfaction overall: Improved satisfaction in 2 RCTs (n=144, p=0.02 and p<0.001) with the use of hyaluronidase, but no difference in another study (1 RCT; n= 20, p=0.96). • **Akinesia** Quicker onset and rate of akinesia with hyaluronidase vs control, but difference may be clinically negligible. Rowley (2000) reported that the degree of akinesia and reduction of eyelid movement, measured 10 minutes after administration of the anaesthetic, was significantly better (p<0.01) in the hyaluronidase group with higher rates of complete akinesia in the treatment group (40) versus the control group (10) out of 150 study participants. Swathi (2018) reported no statistically significant difference between the groups (p = 0.22, 0.68 and 0.98). This difference can be explained by surgery in Swathi being performed by experienced consultants and using a subjective score of akinesia depending on the surgeon's assessment while Rowley had surgeons of varying experience and used an objective scoring system. Swathi also excluded all patients at risk of complications.

QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [X] Low [ ] 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	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [ ] None [X]	Surgical complications were similar in both groups and not felt to be related to the agent used. The systematic review found no evidence of harm attributed to the use of hyaluronidase. Rüschen(2018)
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [X]	For extracapsular surgery, which, is done predominantly at District care level by less experienced doctors, a single instrument is used and surgeons do not have both hands available to keep the eye stable. When non-specialists and trainees do surgery, akinesia is of utmost importance to prevent complications. In the case of phaco surgery, two instruments are used and surgeons have both hands available to keep the eye still. In the studies reviewed phacoemulsification was the method of surgery used in the vast majority of cases. Intra-orbital eye pressure: the use of hyaluronidase facilitates improved tissue penetration into the orbit which results in less pressure and exudate which facilitates improved surgical management. A high coincidence rate exists between sharp rise of IOP and undesirable intraoperative complications such as: shallowing of anterior chamber, herniation of iris through incision site and stromal corneal oedema. Javrishvili (2021))
THERAPEUTIC INTERCHANGE	**Therapeutic alternatives available:** n/a	n/a
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	Hyaluronidase is SAHPRA-registered and available on the market.
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [X] Uncertain [ ]	**Price of medicines/ treatment course –** **Medicine** | **Tender price *** | **SEP**100%** | **SEP ** 60%** Hyaluronidase (1500IU) | R391.18 | R480.25 | R288.15 *Contract circular HP07-2020DAI, August 2022: Hyaluronidase 1500 IU = R391.18 and 150 IU = R39.18. ** SEP database, 31 August 2022: Hyaluronidase 1500 IU = R4802.52 and 150IU = R480.25 **Actual Current Usage** July 2020-October 2022 (28 months): 2012 vials at a cost of R848739.58 (Average spend = R30 312 per month and R363 745 per annum) **Cost per patient:**

		Depends on the operating list as 1 vial can be used for 10 patients: If used for 1 patient cost is: R391.18 and for 10 patients R39.12 per patient. **Other resources:** n/a
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	See above.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	

Version	Date	Reviewer(s)	Recommendation and Rationale

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Appendix 1: Search Strategy

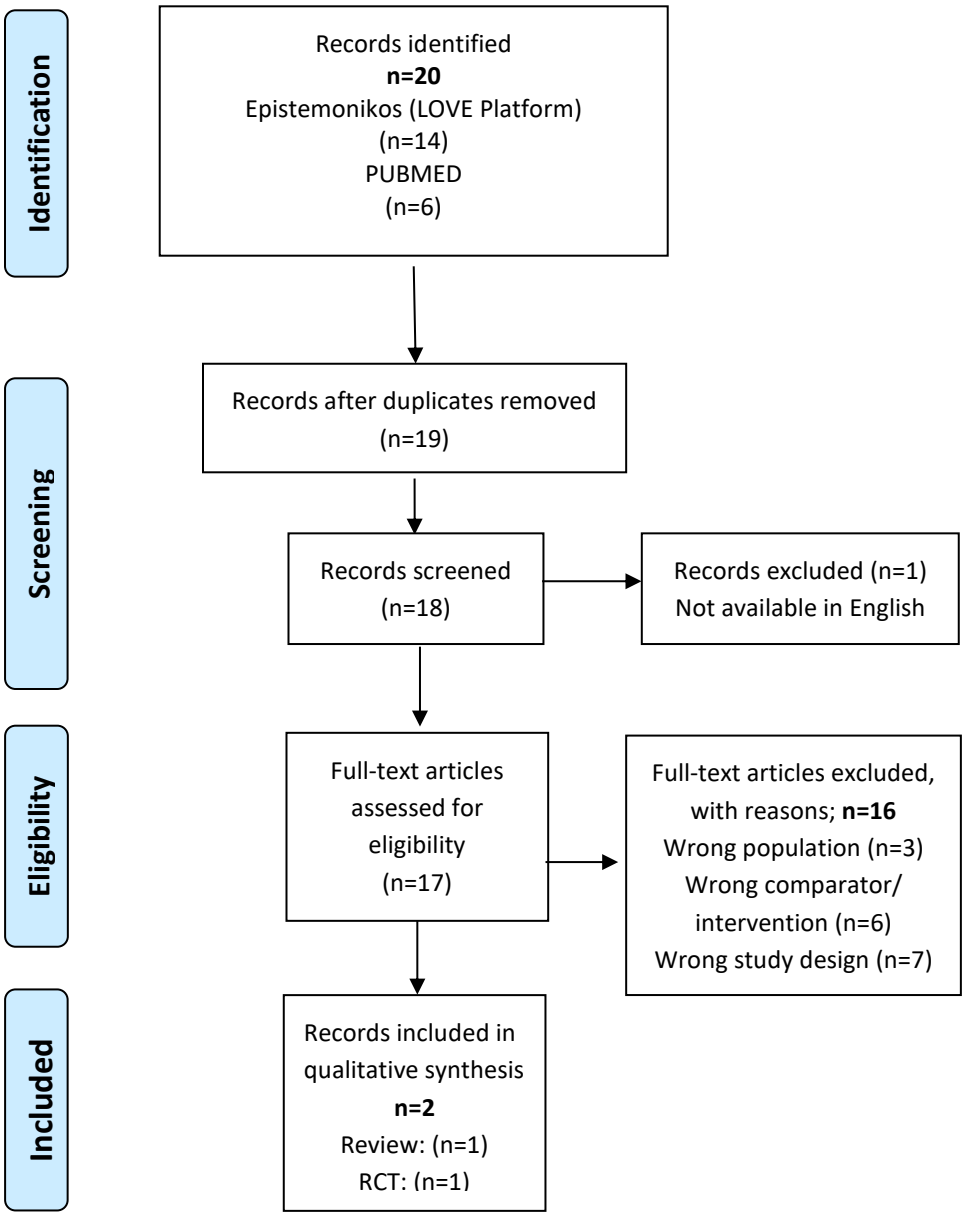
A: PUBMED

SEARCH	QUERY	RESULTS
#16	Filters: from 2017/5/1 - 2022/8/3	14
#15	#13 AND #14	154
#14	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	4,792,867
#13	#4 AND #7 AND #11 AND # 12	250
#12	Search: Hyaluronoglucosaminidase [Mesh] OR hyaluronidase [tiab] OR vitrase [tiab] OR wydase [tiab] or hyalase [tiab] or hylenex [tiab]	12,267
#11	#8 OR #9 0R #10	58,927
#10	Search: Anesthesia, Local [Mesh] OR local anaesthe* [tiab] OR local anesthe*[tiab]	55,168
#9	Search: Nerve Block [Mesh] OR Lidocaine [Mesh] OR Lidocaine [tiab] OR Lignocaine [tiab] OR Mepivacaine [Mesh] OR Isocaine [tiab] Bupivacaine [Mesh] OR Marcain* [tiab]	4,902
#8	Search: peribulbar block [tiab] OR retrobulbar block [tiab] OR sub-tenon block [tiab] or subtenon* [tiab]	1,594
#7	#5 OR #7	4,581,315
#6	transplant* [Mesh] OR graft* [tiab] or extract* [tiab] OR cataract [tiab] OR refractive [tiab] OR oculoplast* [tiab] OR ophthalmosurg*[tiab]	1,819,502
#5	surg*[tiab] OR operat*[tiab]	3,074,295
#4	#1 OR #2 OR #3	2,620,067
#3	Search: glaucoma [Mesh] OR glaucomas [tiab] OR conjuncti*[tiab] OR uveitis [Mesh] OR uveitides [tiab] OR macula* oedema [tiab] OR macular edema [Mesh] OR strabismus [Mesh] or squint [tiab] OR astigmati* [tiab] OR myopia [Mesh] OR myopi* [tiab] OR Hyperopia [Mesh] OR hypermetropia [tiab] OR trachoma [Mesh]	297,541
#2	Search: **visual [tiab] OR vision [tiab] OR sight [tiab] or see* [tiab] or view* [tiab] or blind*[tiab]**	1,493,276
#1	Search: Eye [Mesh] OR Ophthalm* [tiab] OR Vision, ocular [Mesh] OR ocular [tiab] OR Cornea* [Mesh] OR retin* [Mesh] OR Ora serrata [tiab] OR sclera* [Mesh] OR vitreous body [Mesh] OR vitre*[tiab] OR iris [Mesh] OR pupil [tiab] OR orbit*[Mesh] OR eye socket [tiab] OR choroid* [Mesh] OR intraocular [tiab] OR intra-ocular [tiab] OR extraocular [tiab] OR extra-ocular [tiab] OR monocular [tiab] OR oculo* [tiab] OR oculi* [tiab] OR optic* [tiab]	1,215,341
Output: 14 records retrieved, 12 excluded as PICO criteria not met, 2 records selected for inclusion (1 systematic review and 1 RCT)		

B: Epistemonikos

Search strategy: (title:((title:(hyaluronidase) OR abstract:(hyaluronidase)) AND (title:(ophthalmic surgery) OR abstract:(ophthalmic surgery))) OR abstract:((title:(hyaluronidase) OR abstract:(hyaluronidase)) AND (title:(ophthalmic surgery) OR abstract:(ophthalmic surgery)))) Search restricted to systematic reviews
Output: 6 records and all excluded - 1 record retrieved from the PUBMED search (duplicate), 1 record (1999 RCT) only available in Italian and 4 records did not meet the PICO criteria

Appendix 2: PRISMA flowchart



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/

Appendix 3: Characteristics of included studies

Author, date	Type of study	Population (n)	Comparators	Primary outcome	Effect sizes	Comments

Rüschen H *et al.* Use of hyaluronidase as an adjunct to local anaesthetic eye blocks to reduce intraoperative pain in adults (Review). Cochrane Database Syst Rev. 2018 Mar 2;3(3):CD010368.	Systematic review of 7 RCTs (n=500)
	
	Studies conducted in UK (4 RCTs), Germany (1 RCT), Brazil (1 RCT) and Iran (1 RCT)
		n=500
		
		Study participants:
		Adults, ≥ 18 years, presenting for ophthalmic surgery undergoing a retrobulbar, peribulbar or sub-Tenon block.
		
		Age range: 66 to 77 years.
		
		Gender: Studies were balanced with regards to gender.
			Local anaesthetic eye blocks containing hyaluronidase
			
			vs.
			
			Local anaesthetic eye blocks containing no hyaluronidase
			
			Dose: 15 to 150 IU/mL.
				Primary outcome:
				Intraoperative pain, as measured by analogue rating scales (measured on day of surgery).
				
				Secondary outcomes:
				• Incidence of harm (narrative).
				• Participant satisfaction
				• Surgical satisfaction
				• Economic outcomes or cost calculations (narrative)
					Hyaluronidase *vs* no hyaluronidase:
					
					• **Intraoperative pain** (reported dichotomous): 0.25% vs 0.31% (RR 0.83; 95% 0.48, 1.42), 4 RCTs (n=289), *low certainty evidence*
					
					• **Incidence of harm:** NR
					
					• **Participant satisfaction:** Increased satisfaction in treatment group; 2 RCTs (n=122), p<0.05; *moderate certainty evidence*
					
					• **Surgical satisfaction:** Increased satisfaction in treatment group in two RCTs, but no difference between groups in one RCT; n=141, *moderate certainty evidence*
					
					• **Economic outcomes or cost calculations:** NR
						• AMSTAR 2 assessed as high-quality SR
						• *Overall risk of bias:* **Low** to **moderate risk**
						  ○ *Randomisation (and allocation concealment)*: **Low** to **moderate risk**
						  ○ *Missing outcome data*: **Low** to **moderate risk**
						  ○ *Performance bias (blindingof the (patients/personnel):* **Low** to **moderate risk**
						  ○ *Measurement of the outcome (blinding of the assessors):* **Low risk**
						  ○ *Selection of the reported results:* **Low risk**
						• High heterogeneity of data for patient and surgical satisfaction prevented metanalysis of data.
						• Akinesia was not reported on, as the authors of the review initially considered akinesia as an important outcome measure (prioritized over analgesia). Authors reasoned that the majority of surgeons can carry out most operations without depending on fully established akinesia. It was, however, acknowledged that hyaluronidase may be needed where profound akinesia is required for more difficult operations or for training purposed.

Swathi N *et al*. Does the addition of hyaluronidase improve the quality of peribulbar anesthesia in cataract surgery? A randomized double blinded study. Saudi J Ophthalmol. 2018 Jul-Sep;32(3):204-210.	Randomised Double Blinded Study. Single-centre, cataract surgery performed over 15-month period (February 2015–May 2016) by the author, SN, a qualified specialist/ consultant ophthalmologist.	n=202 n1 =100 (no HYA) n2=102 (HYA) *Inclusion criteria:* Adult patients reporting for senile cataracts (first eye only). *<u>Exclusion criteria:</u>* *-First eye only:* Patients with pre-existing pathology where complicated surgery was expected; Pre-existing extra ocular movement restriction and requiring sedation/ general anaesthesia or with systemic contraindication to the use of adrenaline in 1:200000 concentration as noted by the physician during pre-operative work up; *-One-eyed patients:* inflamed eye like phacolytic, phacomorphic glaucomas; pupillary dilatation of <6 mm requiring iris manipulation to	3 ml of 2% lignocaine and adrenaline (1:200000) and 2ml of 0.5% bupivacaine with or without hyaluronidase Group 1 without and Group 2 with hyaluronidase (50IU/ml)	• Surgeons' score for akinesia • Patients' score for analgesia • Augmentation of block • Extra ocular movements on first post-operative day.	*<u>Control: No Hyaluronidase vs Treatment hyaluronidase:</u>* **Unsatisfactory akinesia graded as moderate movements or more by the operating surgeon**: Control: :11/100 (11%) vs Treatment :9/102 (8,8%) , difference of 2.2% **Requirement of additional anaesthesia (as ocular movement):** *Peribulbar and adjunctive subconjunctival (if needed)* Control: 9/100 (9%) Treatment: 5/102 (4,9%) Difference: 4,1% more in Control. (p=0.3) *Peribulbar injection:* Control: 7/100(7%) Treatment : 1/102 (2%) Difference: 5% more in Control. *Subconjunctival injection:*Control : 2/100(2%) Treatment : 3/102 (2,9%)	• *Overall risk of bias:* **Low risk** ○ *Randomisation*: **Low risk** ○ *Deviations from intervention:* **Low risk** ○ *Missing outcome data:* **Low risk** ○ *Measurement of the outcome:* **Low risk** ○ *Selection of the reported result(s):* **Low risk** • Blocks and surgery performed by experienced specialist surgeons on low risk patients in whom no complications were anticipated. • No objective measurement of akinesia done. • Surgical Complications: Posterior capsule rupture: Treatment group: 4, Control Group: 2. p=0,8. Iridodialysis: treatment Group:1. Control group :2. Intraoperative complications not attributed to the anaesthetic solution.

		deliver the nucleus.			Difference: 0,9% more in Treatment. **Pain Score more than 6 at the beginning of surgery:** Control :7/100 (7%) Treatment: 8/102 (7,8%) Difference: 0,8% more in Treatment Akinesia: 0.68 vs 0.98, p=0.22 Analgesia/ anesthetic augmentation: 0.44 vs 0.09, p=0.3 Onset of akinesia and analgesia: Earlier in Group 2 (p = 0.004 and p = 0.005 respectively)	

Abbreviations: HYA = hyaluronidase;

Appendix 4: Characteristics of study (Rowley et al, 2000) not reviewed by Ruschen et al (2018)

Author, date	Type of study	Population (n)	Comparators	Primary outcome	Effect sizes	Comments
Rowley et al. Sub-Tenon's local anaesthesia: the effect of hyaluronidase. British Journal of Ophthalmology 2000;84(4):435-6	Prospective, randomized double blind study performed in a single hospital.	n=150 n1=76 with HYA n2=74 without HYA Inclusion criteria: Patients (age 37-93) scheduled for elective cataract surgery Exclusion: Patients who would not be able to cooperate or safely undergo local anaesthesia. No exclusions for expected complicated surgery.	Hyaluronidase compared to no hyaluronidase (placebo) Both groups received 3 ml lignocaine 2% and adrenaline 1:200 000 with the hyaluronidase group having (30IU/ml) hyaluronidase added	**Akinesia and eyelid movement** was assessed by the ophthalmologist administering the block 10 minutes after administration using a 4 point scale for akinesia and a 3 point score for eyelid movement. (Higher scores allocated to absent movement.)	Akinesia score:(p<0.01) Hyaluronidase:2.32 No Hyaluronidase:1.43 Post injection pain score: (p not provided) Hyaluronidase:2.26 No Hyaluronidase:1.95 Post operative pain score: (p not provided) Hyaluronidase:1.04 No Hyaluronidase:1.03	• *Overall risk of bias:* **Low risk** ○ *Randomisation*: **Low risk** ○ *Deviations from intervention:* **Low risk** ○ *Missing outcome data:* **Low risk** ○ *Measurement of the outcome:* **Low risk** ○ *Selection of the reported result(s):* **Low risk** This study was part of the included studies for both the NICE Guideline review and the Cochrane systematic review. Both the reviews only

				Pain during administration of the block and perioperatively using a Visual Pain Analogue scale by a trained ophthalmic theatre nurse		considered the pain outcomes and not those related to akinesia. Provided objective assessment of akinesia 10 minutes after the block was performed. The incidence of surgical complications was the same in both groups with 1 case of posterior capsule rupture and 2 cases of incomplete capsulorhexis in each group. In none of these cases were the complications assessed as being due to the quality of the block.

Appendix 5: Excluded studies

	Author, date	Study type	Reason for exclusion
1	Khokhar S, et al. Intraoperative aberrometry in cataract surgery with topical versus peribulbar anesthesia. Indian J Ophthalmol. 2020 May;68(5):776-779.	NRSI	PICO criteria not met (wrong intervention)
2	Sharma DSC, et al. Use of hyaluronidase in plastic surgery: A review. J Plast Reconstr Aesthet Surg. 2021 Jul;74(7):1610-1614.	Review article	PICO criteria not met (wrong population)
3	Ibrahim M, et al. Efficacy of midazolam addition to local anesthetic in peribulbar block: Randomized controlled trial. Anaesthesist. 2019 Mar;68(3):143-151.	RCT	PICO criteria not met (wrong intervention)
4	El-Emam EM, et al. Efficacy of Ultrasound-Guided Caudal Epidural Calcitonin for Patients with Failed Back Surgery Syndrome. Anesth Essays Res. 2020 Jan-Mar;14(1):132-136. doi: 10.4103/aer.AER_98_19. Epub 2019 Aug 2.	RCT	PICO criteria not met (wrong population)
5	Pilger D, et al. Use of topical anaesthesia and peribulbar anaesthesia in Descemets membrane endothelial keratoplasty. Eur J Ophthalmol. 2021 May;31(3):1431-1436. doi: 10.1177/1120672120950935. Epub 2020 Aug 27. PMID: 32854539.	NRSI	PICO criteria not met (wrong comparator)
6	Patil V, et al. Effect of the addition of rocuronium to 2% lignocaine in peribulbar block for cataract surgery. J Anaesthesiol Clin Pharmacol. 2017 Oct-Dec;33(4):520-523.	RCT	PICO criteria not met (wrong intervention/ comparator)
7	El Fawal SM, et al. Minimum effective volume of local anesthetic in peribulbar block: does it differ with the eyeball axial length? Braz J Anesthesiol. 2021 Nov-Dec;71(6):635-641.	NRSI	PICO criteria not met (wrong intervention/ comparator)
8	Mohamed AA, et al. Safety and efficacy of addition of hyaluronidase to a mixture of lidocaine and bupivacaine in scalp nerves block in elective craniotomy operations; comparative study. BMC Anesthesiol. 2018 Sep 15;18(1):129.	RCT	PICO criteria not met (wrong population)
9	Malagola R, et al. Peribulbar anesthesia in sclero-retinal surgery: two quadrants vs single injection. G Chir.2018 Jul-Aug;39(4):227-231.	RCT	PICO criteria not met (wrong intervention/ comparator)
10	Moolagani VR, et al. Ropivacaine plus lidocaine versus bupivacaine plus lidocaine for peribulbar block in cataract surgery: A prospective, randomized, double-blind, single-center, comparative clinical study. J Anaesthesiol Clin Pharmacol. 2019 Oct-Dec;35(4):498-503.	RCT	PICO criteria not met (wrong intervention/ comparator)
11	Hakim KY, et al. Comparative Study between the Efficacy of Fentanyl, Antihistamines, and Dexmedetomidine in Suppressing Photic Sneeze Reflex during Peribulbar Block. Anesth Essays Res. 2019 Jan-Mar;13(1):40-43.	RCT	PICO criteria not met (wrong intervention/ comparator)
12	Alsaeid MA. Dexamethasone versus Hyaluronidase as an Adjuvant to Local Anesthetics in the Ultrasound-guided Hydrodissection of the Median Nerve for the Treatment of Carpal Tunnel Syndrome Patients. Anesth Essays Res. 2019 Jul-Sep;13(3):417-422.	RCT	PICO criteria not met (wrong population)
13	Costa P, et al. loco-regionali in oculistica: monofarmacologici o miscela con jaluronidasi? Studio prospettico randomizzato [Loco-regional block in ophthalmic surgery: single drug or drug combination with hyaluronidase? Randomized prospective study]. Minerva Anestesiol. 1999 Nov;65(11):775-83. Italian.	RCT	Not available in English
14	Rüschen H, et al. Use of hyaluronidase as an adjunct to local anaesthetic eye blocks to reduce intraoperative pain in adults. Cochrane Database Syst Rev. 2018 Mar 2;3(3):CD010368.	SR	Duplicate
15	Sarvela PJ. Comparison of regional ophthalmic anesthesia produced by pH-adjusted 0.75% and 0.5% bupivacaine and 1% and 1.5% etidocaine, all with hyaluronidase. Anesth Analg. 1993 Jul;77(1):131-4.	NRSI	PICO criteria not met (wrong intervention/ comparator)
16	Sarvela PJ, et al. Comparison of pH-adjusted bupivacaine 0.75% and a mixture of bupivacaine 0.75% and lidocaine 2%, both with hyaluronidase, in day-case cataract surgery under regional anesthesia. Anesth Analg. 1994 Jul;79(1):35-9.	NRSI	PICO criteria not met (wrong intervention/ comparator)
17	Johnson DA. Persistent vertical binocular diplopia after cataract surgery. Am J Ophthalmol. 2001 Dec;132(6):831-5.	NRSI	PICO criteria not met (prevalence study)
18	Pacella E, et al. Levobupivacaine vs. racemic bupivacaine in peribulbar anaesthesia: a randomized double blind study in ophthalmic surgery. Eur Rev Med Pharmacol Sci. 2010 Jun;14(6):539-44. PMID: 20712261.	RCT	PICO criteria not met (wrong intervention/ comparator)

NRSI=non-randomized study of interventions; RCT=randomized controlled study; SR=systematic review

Appendix 6: AGREE 2 appraisal summary - NICE Guideline, 2017

Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Overall Assessment
NICE (2017) Clinical Guidelines for cataract surgery	94%	83%	79%	89%	77%	58%	92%

Domain 1: Scope and purpose
Domain 2: Stakeholder involvement
Domain 3: Rigour of development
Domain 4: Clarity of presentation
Domain 5: Applicability
Domain 6: Editorial independence
OA: overall assessment

Appendix 7: AMSTAR 2 assessment of Rüschen et al, 2018 using the AMSTAR 2 tool (Shea 2017)[1]

No	Criteria	Yes/ Partial Yes/ No	Comment(s)
1	Research questions and inclusion criteria for the review included the components of PICO	Yes	-
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes	https://doi.org/10.1002/14651858.CD010368
3	Review authors explained selection of the study designs for inclusion in the review	No	RCT only used without explicit motivation
4*	Review authors used a comprehensive literature search strategy	Yes	-
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	-
7	Review authors provided a list of excluded studies and justify the exclusions	Yes	Discrepancies resolved by discussion
8*	Review authors described the included studies in adequate detail	Yes	-
9	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes	-
10*	Review authors reported on the sources of funding for the studies included in the review?	Yes	-
11	For meta-analyses, review authors used appropriate methods for statistical combination of results	Yes	-
12*	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes	-
13	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes	-
14*	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	-
15	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	Yes	-
16*	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	-

** Critical domains*

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies
(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Systematic review by Rüschen et al was assessed to be of high quality.
Rationale: There was only one non-critical weakness and thus the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

[1] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.