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Immediate sequential bilateral surgery versus delayed sequential bilateral surgery for cataracts (Review)

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[Intervention Review]

Immediate sequential bilateral surgery versus delayed sequential bilateral surgery for cataracts

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ABSTRACT

Background

Age-related cataract affects both eyes in most cases. Most people undergo cataract surgery in both eyes on separate days, referred to as delayed sequential bilateral cataract surgery (DSBCS). An alternative procedure involves operating on both eyes on the same day, but as two separate procedures, known as immediate sequential bilateral cataract surgery (ISBCS). Potential advantages of ISBCS include fewer hospital visits for the patient, faster visual recovery, and lower healthcare costs. Nevertheless, concerns exist about possible bilateral, postoperative, sight-threatening adverse effects with ISBCS. Therefore, there is a clear need for evaluating evidence regarding the safety, effectiveness, and cost-effectiveness of ISBCS versus DSBCS.

Objectives

To assess the safety of ISBCS compared to DSBCS in people with bilateral age-related cataracts and to summarise current evidence for the incremental resource use, utilities, costs, and cost-effectiveness associated with the use of ISBCS compared to DSBCS in people with bilateral age-related cataracts (primary objectives). The secondary objective was to assess visual and patient-reported outcomes of ISBCS compared to DSBCS in people with bilateral age-related cataracts.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register; 2021, Issue 5); Ovid MEDLINE; Ovid Embase; the ISRCTN registry; ClinicalTrials.gov; the WHO ICTRP; and DARE and NHS EED on the CRD Database on 11 May 2021. There were no language restrictions. We limited the searches to a date range of 2007 onwards.

Selection criteria

We included randomised controlled trials (RCTs) to assess complications, refractive outcomes, best-corrected distance visual acuity (BCDVA) and patient-reported outcome measures (PROMs) with ISBCS compared to DSBCS. We included non-randomised (NRSs), prospective, and retrospective cohort studies comparing ISBCS and DSBCS for safety assessment, because of the rare incidence of important adverse events. To assess cost-effectiveness of ISBCS compared to DSBCS, we included both full and partial economic evaluations, and both trial-based and model-based economic evaluations.

Data collection and analysis

We used standard Cochrane methodological procedures and assessed risk of bias for NRSs using the ROBINS-I tool. For cost-evaluations, we used the CHEC-list, the CHEERS-checklist, and the NICE-checklist to investigate risk of bias. We assessed the certainty of evidence with the GRADE tool. We reported results for economic evaluations narratively.

Main results

We included 14 studies in the review; two RCTs, seven NRSs, and six economic evaluations (one study was both an NRS and economic evaluation). The studies reported on 276,260 participants (7384 for ISBCS and 268,876 for DSBCS) and were conducted in Canada, the Czech Republic, Finland, Iran, (South) Korea, Spain (Canary Islands), Sweden, the UK, and the USA. Overall, we considered the included RCTs to be at 'high to some concerns' risk of bias for complications, 'some concerns' risk of bias for refractive outcomes and visual acuity, and 'high' risk of bias for PROMs. The overall risk of bias for NRSs was graded 'serious' regarding complications and 'serious to critical' regarding refractive outcomes.

With regard to endophthalmitis, we found that relative effects were estimated imprecisely and with low certainty, so that relative estimates were not reliable. Nonetheless, we found a very low risk of endophthalmitis in both ISBCS (1/14,076 participants) and DSBCS (55/556,246 participants) groups. Based on descriptive evidence and partially weak statistical evidence we found no evidence of an increased risk of endophthalmitis with ISBCS. Regarding refractive outcomes, we found moderate-certainty (RCTs) and low-certainty (NRSs) evidence there was no difference in the percentage of eyes that did not achieve refraction within 1.0 dioptre of target one to three months after surgery (RCTs: risk ratio (RR) 0.84, 95% confidence interval (CI) 0.57 to 1.26; NRSs: RR 1.02, 95% CI 0.60 to 1.75). Similarly, postoperative complications did not differ between groups (RCTs: RR 1.33, 95% CI 0.52 to 3.40; NRSs: 1.04, 95% CI 0.47 to 2.29), although the certainty of this evidence was very low for both RCTs and NRSs. Furthermore, we found low-certainty (RCTs) to very low-certainty (NRSs) evidence that total costs per participant were lower for ISBCS compared to DSBCS, although results of individual studies could not be pooled. Only one study reported on cost-effectiveness. This study found that ISBCS is cost-effective compared to DSBCS, but did not measure quality-adjusted life years using preferred methods and calculated costs erroneously. Finally, regarding secondary outcomes, we found limited evidence on BCDVA (data of two RCTs could not be pooled, although both studies individually found no difference between groups (very low-certainty evidence)). Regarding PROMs, we found moderate-certainty evidence (RCTs only) that there was no difference between groups one to three months after surgery (standardised mean difference −0.08, 95% CI −0.19 to 0.03).

Authors' conclusions

Current evidence supports there are probably no clinically important differences in outcomes between ISBCS and DSBCS, but with lower costs for ISBCS. However, the amount of evidence is limited, and the certainty of the evidence was graded moderate to very low. In addition, there is a need for well-designed cost-effectiveness studies.

PLAIN LANGUAGE SUMMARY

Surgery on both eyes on the same day or on different days: which works better to treat cataract in both eyes?

Key messages

- Current evidence supports there may be no important difference between surgery on both eyes on the same day (ISBCS) and surgery on different days (DSBCS) for the following clinical outcomes: eye (ocular) infection (endophthalmitis, a severe, sight-threatening but rare complication), spectacle correction after surgery (refraction), complications, vision with spectacle correction (if needed), and patient-reported outcomes (PROMs; questionnaires on vision).

- Current evidence supports the costs for ISBCS are lower compared to DSBCS, but evidence on the balance between the costs and how well it works (cost-effectiveness) was lacking.

- Overall, the amount and quality of the evidence was limited.

What is cataract and how is it treated?

Age-related cataract is a natural ageing process of the lens of the eye, in which the lens becomes cloudy and vision decreases. The only way to treat cataract is by surgery. During surgery, the clouded lens is removed and replaced by an artificial lens, implanted in the eye. Currently, most people undergo cataract surgery on both eyes on different days, with a period of days, weeks, or even months between surgeries, called delayed sequential bilateral cataract surgery (DSBCS). However, it is also possible to have cataract surgery on both eyes on the same day, called immediate sequential bilateral cataract surgery (ISBCS).

Potential advantages to ISBCS include fewer visits to the hospital, faster visual recovery, and lower healthcare costs. However, there are also potential disadvantages, such as developing complications in both eyes. Also, in ISBCS, outcomes of the first eye cannot be used when performing second-eye surgery, which may result in worse refractive outcomes (increased spectacle dependence).

What did we want to find out?

We wanted to find out if cataract surgery on both eyes on the same day is as safe, effective, and cost-effective as having surgery on both eyes on different days.

What did we do?

We searched for studies that looked at outcomes of ISBCS compared to DSBCS. We also searched for studies that looked at the balance between costs and outcomes for ISBCS compared to DSBCS (cost-effectiveness). We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 14 studies that involved 276,260 people (7384 who had ISBCS and 268,876 who had DSBCS). The studies were conducted in Canada, the Czech Republic, Finland, Iran, (South) Korea, Spain (Canary Islands), Sweden, the UK, and the USA. Most studies lasted for around three months.

Main results

- Endophthalmitis: the type of surgery (ISBCS or DSBCS) may make little to no difference in the occurrence of endophthalmitis in one eye (up to six weeks after surgery). None of the studies reported endophthalmitis in both eyes, but this event is most likely too rare to be detected by these studies.

- Refractive outcomes: there is probably little to no difference in refractive outcomes at one to three months after surgery with ISBCS compared to DSBCS.

- Other complications: there may be little to no difference in other complications up to three months after surgery with ISBCS compared to DSBCS, but we are very uncertain about the results.

- Costs: the economic studies in this review reported lower costs for ISBCS compared to DSBCS. One study reported that ISBCS is cost-effective compared to DSBCS, but we are very uncertain about the results.

- Best-corrected distance visual acuity (BCDVA; vision with spectacle correction if needed): the type of surgery (ISBCS or DSBCS) may have little to no effect on BCDVA at one to three months after surgery, but we are very uncertain about the results.

- PROMs (measured in questionnaires): the type of surgery (ISBCS or DSBCS) probably makes little to no difference in PROMs at one to three months after surgery.

What are the limitations of the evidence?

Overall, we had moderate to very little confidence in the evidence (endophthalmitis: little confidence, refractive outcomes: little to moderate confidence, complications: not confident, costs: little to no confidence, BCDVA: not confident, and PROMs: moderate confidence).

Our confidence is limited because:

- the evidence on endophthalmitis was based on few cases of endophthalmitis;

- the studies assessed complications in different ways;

- there were not enough studies to be certain about refractive outcomes and complications;

- studies on costs reported costs for only one hospital and included different funding sources;

- the studies assessed BCDVA in different ways and there were not enough studies to be certain about the results;

- there were concerns regarding the possibility that people in the studies were aware of what treatment they were getting, and not all studies provided data about everything that we were interested in (most outcomes).

How up to date is this evidence?

The evidence is up-to-date to 11 May 2021.

SUMMARY OF FINDINGS

Summary of findings 1. ISBCS compared to DSBCS in people with bilateral age-related cataracts (RCTs)

ISBCS compared to DSBCS in people with bilateral age-related cataracts (RCTs)

Patient or population: people with bilateral age-related cataracts (RCTs)

Setting: ophthalmic surgical centre
Intervention: ISBCS
Comparison: DSBCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DSBCS	Risk with ISBCS				
Endophthalmitis Follow-up: 6 weeks	0 cases of endophthalmitis in both the ISBCS group (total of 1327 eyes) and the DSBCS group (total of 1286 eyes)		—	1309 (2 RCTs)	⊕⊕⊖⊖ **Low**[a]	Relative effects were not estimable because of the rarity of the event (0 events).[b]
Refraction NOT within 1.0 dioptres of target Follow-up: range 1–3 months	**97 per 1000**	**82 per 1000** (55 to 122)	**RR 0.84** (0.57 to 1.26)	982 (1 RCT)	⊕⊕⊕⊖ **Moderate**[c,d]	b
Complications Follow-up: 3 months	**142 per 1000**	**189 per 1000** (74 to 482)	**RR 1.33** (0.52 to 3.40)	1305 (2 RCTs)	⊕⊖⊖⊖ **Very low**[e,f,g]	Results represent postoperative complications. Intraoperative complications: occurred in 28/1327 (2.1%) ISBCS eyes and 38/1286 (3.0%) DSBCS eyes (RR 0.75, 95% CI 0.47 to 1.21) with an absolute effect of 7 fewer per 1000 (ranging from 16 fewer to 6 more).[b]
Total costs per participant	ISBCS: USD 4811 DSBCS: USD 6748		—	(1 RCT)	⊕⊕⊖⊖ **Low**[h,i]	Available data for only 1 study: reported total costs from a societal perspective (costs converted to 2017 USD). Pooled results not available.
Total costs per QALY	No data available		—	—	—	Outcome not reported for RCTs.
BCDVA Follow-up: range 1–3 months	Study 1: proportion of eyes with BCDVA 20/25 or better was 376/488 (77%) for ISBCS vs 336/494 (68%) for DSBCS		—	(2 RCTs)	⊕⊖⊖⊖ **Very low**[j,k]	Data were too heterogeneous to allow comparison. 1 study reported proportion of eyes with BCDVA of 20/25 or better, 1 study reported me-

	Study 2: median (range) BCDVA of 20/22 (LP, 20/20) for ISBCS vs 20/22 (LP, 20/20) for DSBCS					dian BCDVA. Both RCTs found no significant difference in BCDVA between groups.[b]
PROMs Follow-up: range 1–3 months	—	**SMD 0.08 SD lower** (0.19 lower to 0.03 higher)	—	1297 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[l]	m

*__The risk in the intervention group__ (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).

BCDVA: best-corrected distance visual acuity; **CI:** confidence interval; **DSBCS:** delayed sequential bilateral cataract surgery; **ISBCS:** immediate sequential bilateral cataract surgery; **LP:** light perception; **PROM:** patient-reported outcome measure; **QALY:** quality-adjusted life year; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation; **SMD:** standardised mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423934485069557583.

[a]Downgraded two levels for imprecision: sample sizes and number of events were too small to adequately measure the outcome and estimate the effect.
[b]Results were on the eye level (both eyes of 1 participant included).
[c]Lundström 2018.
[d]Downgraded one level for imprecision: the optimal information criterion was met. However, the CI failed to exclude important benefit or harm, since a reduction of 43% not falling within 1.0 dioptres or an increase of 26% not falling within 1.0 dioptres remains plausible (while currently accepted percentages within 1.0 dioptres of target are about 90% as reported by Lundström 2018).
[e]Downgraded one level for risk of bias: the RCT that contributed the most data on complications was at high risk of bias for this outcome due to non-adherence to the intervention (because of surgeon preference to perform second eye surgery on another day). This is likely to be as a result of increased risk during surgery or intraoperative complications, thereby influencing the confidence in the estimate of the effect for intraoperative or postoperative complications, or both.
[f]Downgraded one level for inconsistency: $I^2 = 65\%$.
[g]Downgraded one level for imprecision: the CI failed to exclude important benefit or important harm.
[h]Downgraded one level due to moderate to high overall risk of bias.
[i]Downgraded one level for indirectness: results included only one single hospital (indirectness as a result of the setting in which the interventions were performed).
[j]Downgraded one level for inconsistency and one level for indirectness (of the outcome): data were too heterogeneous to allow comparison. At one to three months after surgery, Sarikkola 2011 reported the proportion of participants with a BCDVA of 20/25 or better, whereas Serrano-Aguilar 2012 reported the median BCDVA with range.
[k]Downgraded one level for imprecision: only one of two studies reported a median with range for this outcome, and the reported range was very wide (included both LP and 20/20 vision).
[l]Downgraded one level for risk of bias: participants were aware of the intervention received and PROMs are a subjective measurement that could be influenced by knowledge of treatment allocation. This lowers the confidence in the effects.
[m]Results were on participant level.

Summary of findings 2. ISBCS compared to DSBCS in people with bilateral age-related cataracts (NRSs)

ISBCS compared to DSBCS in people with bilateral age-related cataracts (NRSs)

Patient or population: people with bilateral age-related cataracts (NRSs)
Setting: ophthalmic surgical centre
Intervention: ISBCS
Comparison: DSBCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DSBCS	Risk with ISBCS				
Endophthalmitis Follow-up: 6 weeks	**10 per 100,000**	**19 per 100,000** (3 to 120)	**RR 1.97** (0.32 to 12.16)	570,322 (7 observational studies)	⊕⊕⊖⊖ **Low**[a,b,c]	Only 1 NRS was sufficiently large to identify cases of endophthalmitis in both treatment groups. Absolute risk with ISBCS: 0.019% (95% CI 0.003 to 0.12).[d]
Refraction NOT within 1.0 dioptres of target Follow-up: range 1–3 months	**46 per 1000**	**47 per 1000** (27 to 80)	**RR 1.02** (0.60 to 1.75)	946 (3 observational studies)	⊕⊕⊖⊖ **Low**[b,e,f]	[d]
Complications Follow-up: 3 months	**10 per 1000**	**10 per 1000** (5 to 23)	**RR 1.04** (0.47 to 2.29)	25,739 (5 observational studies)	⊕⊖⊖⊖ **Very low**[b,g,h]	Results represent postoperative complications. Intraoperative complications: occurred in 150/7905 (1.3%) ISBCS-treated participants and 12,981/516,662 (0.9%) DSBCS-treated participants (RR 1.27, 95% CI 1.07 to 1.51).[i]
Total costs per participant	4 NRSs that reported total costs per participant found lower costs for ISBCS compared to DSBCS. Only 1 study included cost year (Neel 2014a), and could therefore be converted to 2017 USD. Total costs per participant in this study were USD 3197 (ASC)/USD 4330 (HOPD) for ISBCS and USD 4451 (ASC)/ USD 5962 (HOPD) for DSBCS		—	(4 observational studies)	⊕⊖⊖⊖ **Very low**[j,k]	—
Total costs per QALY	No data available		—	—	—	Only 1 study reported QALYs (Malvankar-Mehta 2013). However, QALYs were not calculated us-

						ing preferred methods and the study was considered to be of critical risk of bias, so that the results of the study could not be used for this review.
BCDVA	—	—	—	—	—	Outcome not included for NRSs.
PROM	—	—	—	—	—	Outcome not included for NRSs.

*__The risk in the intervention group__ (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).

ASC: ambulatory surgical centre; **BCDVA:** best-corrected distance visual acuity; **CI:** confidence interval; **DSBCS:** delayed sequential bilateral cataract surgery; **HOPD:** hospital outpatient department; **ISBCS:** immediate sequential bilateral cataract surgery; **NRS:** non-randomised study; **PROM:** patient-reported outcome measure; **QALY:** quality-adjusted life year; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423962415891828344.

[a] Grzybowski 2021a.
[b]Downgraded one level for risk of bias: multiple studies were graded at an overall high/serious risk of bias. In addition, Herrinton 2017, which mainly determined the presented results, was retrospective and, therefore, at high risk of bias for patient selection, which is likely to lower the confidence in the estimate of the effect.
[c]Downgraded one level for imprecision: the absolute risk with ISBCS was estimated at 0.019% (95% CI 0.003% to 0.12%). Since the upper CI is higher than currently reported rates for unilateral endophthalmitis in the literature, the CI failed to exclude important benefit or harm.
[d]Results were on eye level (both eyes of one participant).
[e]Lundström 2018.
[f]Downgraded one level for imprecision: the optimal information criterion was met. However, the CI failed to exclude important benefit or harm, since a reduction of 40% not falling within 1.0 dioptres or an increase of 75% not falling within 1.0 dioptres remains plausible (while currently accepted percentages within 1.0 dioptres of target were around 90% as reported by Lundström 2018).
[g]Downgraded one level for inconsistency: there was substantial heterogeneity (I^2 = 71%).
[h]Downgraded one level: the CI failed to exclude important benefit or harm.
[i]Results were partially on the participant level (Herrinton 2017) and partially on eye level (all other studies).
[j]Downgraded one level for risk of bias: the economic studies were graded at high risk of bias.
[k]Downgraded at one level due to differences in included cost sources and time horizon employed.

BACKGROUND

Description of the condition

An age-related cataract is characterised by gradual clouding of the crystalline lens. In 2015, unoperated cataracts accounted for 35% of blindness worldwide, indicating that this vision-impairing condition was the leading cause of preventable blindness (Bourne 2017). In most cases, age-related cataract affects both eyes, referred to as bilateral cataracts (Neel 2014a). In contrast to unilateral cases, bilateral cataracts are more likely to cause significant problems in daily activities, such as reading and face recognition, negatively impacting quality of life (QoL) in older people (Harrer 2013; Zuo 2015). In addition, people are more likely to be placed in nursing homes and have falls, resulting in fractures and increased mortality (Chew 2012). Compared to unilateral cases, bilateral cataracts also negatively affect vision-specific functions. Treatment of both eyes results in higher patient satisfaction, and greater improvement of visual acuity and vision-related QoL compared to treating only one eye (Chew 2012; Shekhawat 2017).

Description of the intervention

Cataracts are not generally amenable to prevention, but cataract surgery can effectively restore vision. Cataract surgery involves removing the clouded lens and replacing it with an artificial intraocular lens (IOL), and is one of the most common operations worldwide. Given the ageing population, the cataract surgery rate is expected to rise, placing an even greater burden on healthcare systems and limiting access to care (Erie 2007). At present, most patients undergo cataract surgery in both eyes on separate days, referred to as delayed sequential bilateral cataract surgery (DSBCS). An alternative procedure involves operating on both eyes on the same day, as two separate procedures, known as immediate sequential bilateral cataract surgery (ISBCS). Despite potential lower healthcare costs for ISBCS compared to DSBCS due to less turnover time between surgeries, avoidance of additional daycare admission, less use of home care, and a reduction in travel costs, national clinical practice guidelines (e.g. in the US and Canada), often advise limiting ISBCS to exceptional cases only (Leivo 2011; Neel 2014a; O'Brien 2010; Rush 2015). For example, ISBCS may be performed on people requiring general anaesthesia in the presence of bilateral visually significant cataracts (Guidelines and Protocols Advisory Committee 2021; Olson 2017). In contrast, the UK National Institute for Health and Care Excellence (NICE) cataract guidelines advise surgeons to consider offering ISBCS to people in whom there is a low risk of complications (NICE 2017). Still, the main reason for this reluctance for ISBCS among cataract surgeons is concern about the safety and effectiveness of this procedure compared to DSBCS. Therefore, the current review sets out to compare ISBCS and DSBCS with regard to safety, visual outcomes, patient-reported outcome measures (PROMs), and cost-effectiveness.

How the intervention might work

While cataract surgery on one eye is effective in restoring functional vision, studies have shown that cataract surgery of the second eye leads to faster visual rehabilitation, fewer visits to the surgical centre, and further improvement in QoL and patient satisfaction (Frampton 2014; Lundström 2006; Nassiri 2009; Serrano-Aguilar 2012; Shekhawat 2017). Therefore, potential advantages of ISBCS over DSBCS include faster visual rehabilitation, resulting in higher patient satisfaction (Lundström 2006; Nassiri 2009; Serrano-Aguilar 2012). ISBCS also reduces visits to the surgical centre, and may lead to a more efficient use of healthcare resources, and improve access to care by reducing patient turnover time (Leivo 2011; Lundström 2009; Rush 2015). For instance, Leivo and colleagues described a potential saving of 20% regarding operating room floor and wage costs due to lower turnover time for ISBCS compared to DSBCS (Leivo 2011). As for the number of hospital visits, Lundström and colleagues found people treated with ISBCS had on average four visits, while people treated with DSBCS had 7.1 visits on average (Lundström 2009). However, the main reason for delaying surgery on the second eye is the concern of bilateral endophthalmitis, a rare, yet potentially devastating complication, most likely to occur within the first two weeks after surgery. Another reason for delaying surgery on the second eye is the opportunity to evaluate the refractive outcome of the first eye, and if necessary, adjust the plans for surgery of the second eye. Nevertheless, some have argued that due to many advances in the field of cataract surgery, it is now increasingly safe to perform ISBCS, and outcomes may not fall short of DSBCS, provided that patients have been selected carefully, and that surgery is performed in accordance with the ISBCS General Principles for Excellence in ISBCS, 2009 (Arshinoff 2012; Chung 2009; Neel 2014a; Sarikkola 2011; Schwartz 2016). Nonetheless, opponents of ISBCS argue that the potential risk of severe bilateral complications and unexpected refractive outcomes supersede any economic arguments and ease for patients that are associated with ISBCS (Henderson 2012).

Why it is important to do this review

This review is particularly appropriate at the present time, due to the clear need for reliable evidence regarding the safety, effectiveness, and cost-effectiveness of ISBCS versus DSBCS. Comparing ISBCS with DSBCS will help healthcare professionals to evaluate the available evidence on both procedures, and may change their practice. The results may also contribute to the development or adjustment of national guidelines for the treatment of cataracts, since several guidelines currently advise against ISBCS as a standard procedure for bilateral cataracts (Guidelines and Protocols Advisory Committee 2021; Olson 2017). Comparing both surgical procedures in this review may also help people who are considering bilateral cataract surgery to make a more informed decision. Finally, in the face of an ageing population and increasing global healthcare expenditures, there is a clear need to evaluate cost-effectiveness, since even small efficiency gains in the delivery of cataract care may lead to substantial cost savings at the population level.

OBJECTIVES

To assess the safety of ISBCS compared to DSBCS in people with bilateral age-related cataracts and to summarise current evidence for the incremental resource use, utilities, costs, and cost-effectiveness associated with the use of ISBCS compared to DSBCS in people with bilateral age-related cataracts (primary objectives). The secondary objective was to assess visual and patient-reported outcomes of ISBCS compared to DSBCS in people with bilateral age-related cataracts.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) to assess the effects, refractive outcomes, and PROMs of ISBCS compared to DSBCS. Including cluster-randomised trials or cross-over randomised trials was not applicable, since the intervention is allocated on an individual level, and cross-over of interventions is not possible.

Since the incidence of safety data was expected to be rare (e.g. for unilateral or bilateral endophthalmitis), we systematically searched for and included non-randomised studies (NRSs) to assess this subject. In addition, we included prospective and retrospective cohort studies comparing ISBCS and DSBCS for safety assessment. We did not use non-randomised studies (NRSs) for additional data overall.

Finally, to assess cost-effectiveness of ISBCS compared to DSBCS, we included both full (cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses), and partial economic evaluations (cost analyses, cost description studies, and cost-outcome descriptions). Although partial economic evaluations provide limited information (e.g. only costs, only effects of no comparison of interventions), they can provide useful information, especially on topics in which the (expected) difference in effect is small or the new intervention involves better effectiveness. We included trial-based economic evaluations and model-based economic evaluations, in order to provide a complete overview.

We only included studies that were performed in the last 10 years prior to the development of the initial review protocol (i.e. from 2007 onwards), to assure the use of recent safety standards (e.g. use of antibiotics, small-incision surgery). We included all eligible studies, regardless of their publication status. We presented data on RCTs separately from data of comparative NRSs (Reeves 2011).

Types of participants

We included studies that involved adults with bilateral age-related cataracts, who underwent phacoemulsification cataract surgery with artificial IOL implantation in both eyes, either on the same day (ISBCS), or on different days within a varying interval (weeks to months) between surgeries on the first and second eye (DSBCS). We documented in the Characteristics of included studies table when studies included participants with factors known to affect the risk of endophthalmitis (e.g. current ocular, adnexal, or periocular infections; immunocompromised people, people allergic to iodine), refractive surprise (abnormal axial lengths of less than 21 mm or greater than 27 mm, previous refractive surgery, or abnormal keratometry), or complicated surgery (previous ocular surgery, trauma, anatomical abnormalities, or posterior polar cataract).

Types of interventions

Intervention: immediate sequential bilateral cataract surgery (ISBCS).

In this treatment, participants underwent phacoemulsification cataract surgery with implantation of an IOL in both eyes on the same day, during a single operative session.

Comparator: delayed sequential bilateral cataract surgery (DSBCS).

In this treatment, participants underwent phacoemulsification cataract surgery with implantation of an IOL in both eyes on two separate days, and in two separate operative sessions. The interval between the two procedures may vary.

Types of outcome measures

Primary outcomes

- **Adverse events related to bilateral cataract surgery:** (e.g. the proportion of people with severe or sight-threatening endophthalmitis as a bilateral complication of cataract surgery, refractive surprise, or other intra- and postoperative complications).
  - *Severe endophthalmitis:* symptoms associated with endophthalmitis, such as pain or loss of vision, due to aqueous or vitreous infection, with an onset between three days and six weeks postoperatively (Endophthalmitis Study Group 2007), according to the definition in the Endophthalmitis Vitrectomy Study (Doft 2008).
  - *Refraction:* the proportion of eyes in which the achieved spherical equivalent refraction was NOT within 0.5 dioptre and NOT within 1.0 dioptre of target refraction, measured one to three months after surgery.
  - *Intraoperative and postoperative complications:* the proportion of complications (other than bilateral endophthalmitis) that occurred intraoperatively (e.g. capsular rupture, haemorrhage), or postoperatively (e.g. corneal oedema, retinal detachment, cystoid macula oedema), from the procedure to three months' follow-up.
- **Cost-effectiveness or economic evaluations:** total cost per participant, cost per quality-adjusted life year (QALY), or both, over the reported time horizon. If reported, total costs were split into cost categories and over years (if the time horizon exceeded one year). We reported the costs in the currency and year stated in the studies. However, to make the outcomes more comparable, costs were also reported in one common currency (2017 USD). Because costs in different years are less comparable as a result of inflation, we reported costs for one common year. Any costs incurred in another year were converted to a common year (2017) using the consumer price index as reported and advised by the Organisation for Economic Co-operation and Development (OECD). Then, we converted the non-USD currency to 2017 USD (manual calculation) using the Purchasing Power Parity for Gross Domestic Product (PPP for GDP) as reported by the OECD.

Secondary outcomes

- **Visual acuity:** best-corrected distance visual acuity (BCDVA; measured by logMAR or Snellen charts) at baseline (before treatment), and one to three months after surgery. Differences of fewer than 5 letters (0.1 logMAR) were not considered to be clinically important.
- **Patient-related outcome measures (PROMs):** participant satisfaction, vision-specific QoL, and health-related QoL, as measured by visual function and disability questionnaire scores at baseline (before treatment) and one to three months after surgery. We also reported mean change in PROMs between baseline and one to three months after surgery.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases. There were no restrictions to language on the searches and full-paper translations were arranged by Cochrane Eye and Vision through a network of translators. The date parameters for the search were 2007 onwards. The date of the search was 11 May 2021.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 5) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (Appendix 1).
- MEDLINE Ovid (2007 to 11 May 2021) (Appendix 2).
- MEDLINE Ovid – economic search (Appendix 3).
- Embase Ovid (2007 to 11 May 2021) (Appendix 4).
- Embase Ovid – economic search (2007 to 11 May 2021) (Appendix 5).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch) (Appendix 6).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 7).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) (Appendix 8).
- DARE and NHS EED on CRD Database (www.crd.york.ac.uk/CRDWeb/HomePage.asp) (Appendix 9).

Searching other resources

We searched the reference lists of the studies included in the review for both RCTs and NRSs that compared ISBCS and DSBCS.

Data collection and analysis

Selection of studies

Two review authors (LSS and RWPS) independently screened the titles and abstracts identified through the searches, using web-based software (Covidence). We resolved disagreements by discussion. In general, we did not document the citations we considered not relevant at this stage, other than to note their numbers in a flow chart. We obtained full-text copies of potentially relevant studies (as defined in the Types of studies section). Two review authors (LSS and RWPS) independently assessed the full-text copies for inclusion, according to the Criteria for considering studies for this review' section. We resolved disagreements by discussion. Since there was no need for clarification of study eligibility for inclusion, no additional correspondence with investigators was required. We were not masked to the names of the authors, institutions, or journal publication when we screened and selected our studies. We listed all studies excluded at this stage, and provided a brief justification for exclusion. We listed all studies excluded after examination of the full-text in the excluded studies table.

For potentially eligible studies identified in trials registers, we documented the study in the Characteristics of ongoing studies table if the study had a registered completion date within two years of our search, or in the future.

Furthermore, two review authors (LSS and RWPS) screened economic evaluations against eligibility criteria as previously defined for the studies regarding intervention effects (Shemilt 2019). The same two review authors classification of economic evaluations and any links with eligible trials included in the review.

Data extraction and management

Two review authors (LSS and RWPS) independently extracted data, using an Excel template that was based on the online form developed by Cochrane Eyes and Vision and the data extraction parameters as specified in the study characteristics section below. We aimed to report on adjusted measures rather than unadjusted measures, as an attempt to control for confounding. Nonetheless, only unadjusted measures were available for inclusion in the current review. We resolved discrepancies by discussion between the two review authors. We contacted trial investigators for missing data. One review author (LSS) imported all data directly into Review Manager Web, and another review author (RWPS) checked the accuracy of the data import (Review Manager Web).

For economic evaluations, two review authors (LSS and RWPS) independently used an Excel template to collect study characteristics. We resolved discrepancies by discussion. One review author (LSS) imported all data directly into Review Manager Web, and another review author (RWPS) checked the accuracy of the data import (Review Manager Web).

Study characteristics

We collected the following information on study characteristics (Appendix 10).

- Study design: RCT, non-RCT, prospective cohort study, retrospective cohort study, cost-effectiveness study.
- Participants: country, total number, age, sex, inclusion and exclusion criteria, one or both eyes reported.
- Intervention and comparator details: including number of participants (eyes).
- Primary and secondary outcomes: as measured and reported in the trials, adverse events.
- Length of follow-up.
- Date study conducted.
- Funding and conflicts of interest.
- Included on trials registry: yes or no, including registration number if available.

Regarding studies on cost-effectiveness and economic evaluations, we collected the following data.

- Perspective (e.g. health care, insurance, clinical) and time horizon for both costs and effects.
- Healthcare costs, patient and family costs, societal costs, and total costs.
- Effectiveness (utility, QALY).
- Incremental cost-effectiveness ratio (ICER).
- Year of study; details on interventions and comparators; study design and source(s) of resource use; decision-making jurisdiction, geographical and organisational setting (as recommended in Shemilt 2011a).
- Details on sensitivity analyses undertaken, and information about the impact of varying assumptions on the magnitude and direction of the results (as recommended in Shemilt 2011a).

Outcome data

We extracted the following data from each included study for intervention and comparator groups separately.

- Mean, standard deviation (SD), and number of participants – outcomes that were measured by continuous variables (visual acuity, PROMs).
- Number of events and number of participants – outcomes that were measured by dichotomous variables (endophthalmitis, refraction less than 0.5 dioptre and less than 1.0 dioptre, other complications).

If these data were not provided in the article, we retrieved them from other data reported, or we contacted the authors and asked them to provide the required data.

Assessment of risk of bias in included studies

Two review authors (LSS and RWPS) independently assessed the risk of bias in the included studies (i.e. RCTs, NRSs, and economic studies).

For RCTs, we used Cochrane's RoB 2 tool for assessing risk of bias, as outlined in Sterne 2019. For adverse effects outcomes (i.e. endophthalmitis, refractive outcomes, complications), the effect of interest included both the effect of assignment to intervention (intention-to-treat (ITT) effect) and the effect of adhering to the intervention (per-protocol effect), since these may differ in case of deviation from the assigned intervention. We specifically considered and reported on the following domains of bias.

- Bias arising from the randomisation process.
- Bias due to deviations from the intended interventions.
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.

We rated each domain as low risk of bias, some concerns, or high risk of bias. To reach an overall risk of bias judgement, we used signalling questions and algorithms as provided in the RoB 2 tool. We resolved disagreements by discussion. We assessed the risk of bias for the following outcomes.

- Adverse events: complications (endophthalmitis up to six weeks postoperatively and other complications up to three months after surgery).
- Adverse events: refractive outcomes (one to three months after surgery).
- Visual acuity (one to three months after surgery).
- PROMs (one to three months after surgery).

Regarding the management of the assessment of bias, we used the RoB 2 crib sheet and template for completing the assessment, as provided on the riskofbiasinfo.org website.

For NRSs, we used the ROBINS-I tool (Sterne 2016). We specifically considered and reported on the following sources of bias.

- Bias due to confounding.
- Bias in classification of interventions.
- Bias in selection of participants into the study.
- Bias due to deviations from intended interventions: effect of assignment to intervention.
- Bias due to deviations from intended interventions: effect of adhering to intervention.
- Bias due to missing data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.

For these studies, we graded each domain as low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias, or no information on risk of bias. We resolved disagreements by discussion. We assessed the risk of bias using the ROBINS-I tool for the following outcomes.

- Adverse events: complications (endophthalmitis up to six weeks postoperatively and other complications up to three months after surgery)
- Adverse events: refractive outcomes (one to three months after surgery)

After we conducted the first search of studies, we used three NRSs to pilot test the ROBINS-I tool, in order to better understand the spectrum of interventions, co-interventions, and confounders. The following confounders and potential co-interventions were investigated.

- Complications.
  - Confounders: presence of ocular or systemic (or both) comorbidities in general (e.g. diabetes, rheumatic disease, uveitis, glaucoma), factors known to affect the risk of endophthalmitis (e.g. current ocular, adnexal of periocular infections, immunocompromised participants, participants allergic to iodine), factors known to affect risk of complicated surgery (e.g. previous ocular surgery, trauma, anatomical abnormalities, posterior polar cataract, surgeon experience), participant age.
  - Co-interventions: administration of intracameral antibiotics, postoperative administration of anti-inflammatory drugs.
- Refractive outcomes.
  - Confounders: factors known to affect the risk of refractive surprise (e.g. axial length differences between groups, abnormal axial length of less than 21 mm or greater than 27 mm, previous refractive surgery, abnormal keratometry), presence of preoperative visual comorbidities other than cataract (e.g. age-related macular degeneration), biometry measurement techniques (e.g. IOL calculation method (formula) used), type of lens implanted (monofocal, toric, multifocal).
  - Co-interventions: adjustment of IOL power calculation for the second eye, after first eye surgery outcomes.

We used the following approach to evaluate risk of bias in economic evaluations.

- We used Cochrane's RoB 2 tool to assess risk of bias in single, empirical studies that provided clinical data used in included economic evaluations (Higgins 2017).
- We assessed the overall methodological quality of full economic evaluations conducted alongside single, empirical studies by combining the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) statement (Husereau 2013), and

the Consensus on Health Economic Criteria (CHEC) list for assessment of methodological quality of economic evaluations (Evers 2005).

- We assessed the overall methodological quality of model-based economic evaluations by using the CHEERS statement and the checklist of the NICE Guidelines Manual 2014, Appendix H: 'Appraisal checklists: economic evaluations' (NICE 2014).

Measures of treatment effect

We calculated the risk ratio (RR) and 95% confidence intervals (CI) for the following dichotomous outcomes: endophthalmitis, refraction, and intraoperative and postoperative complications. Despite the rareness of endophthalmitis, we did not change the RR to risk difference (because of the potential for an unrealistic perception of good precision) or use Peto's method (because of the large difference in total number of eyes included in both groups). We used the standardised mean difference (SMD) with 95% CIs for PROMs, because of the use of different questionnaires (since the SMD expresses the size of the intervention effect in each study relative to the variability observed in that study). Where possible, we checked for the skewness of continuous data (Altman 1996).

Unit of analysis issues

Multiple observations, due to repeated measurements for the same outcome (e.g. visual acuity, PROMs, refraction), were not an issue in the current review.

Eyes and people

People were randomly allocated, with both eyes, to either intervention or comparator treatments. We could not adjust for within-person correlation, since data were available for all eyes but not for first and second eyes separately for almost all included studies. Additionally, we used participant rather than eye as the unit of analyses for PROMs, since these are measured on a participant level.

Dealing with missing data

If available, we used ITT data from the included studies. If ITT data were not available, we used available-case data, assuming that data were missing completely at random. We assessed whether this assumption was reasonable by collecting data, from each included trial, on the number of participants excluded or lost to follow-up, and reasons for loss to follow-up by treatment group, if reported.

Assessment of heterogeneity

We explored the clinical and methodological heterogeneity by examining the overall characteristics of the studies, in particular the type of participants and types of interventions, to assess the extent to which the studies were similar enough to make pooling study results sensible. We examined the forest plots of study results to see how consistent the results of the studies were, in particular, considering the size and direction of effects. We calculated I^2 statistics, which equals the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (i.e. chance) (Higgins 2002). We considered I^2 values over 50% to indicate substantial inconsistency, but also considered the Chi^2 P value. As this may have low power, especially in case of limited numbers of studies, we considered $P \leq 0.10$ to indicate statistical significance of the Chi^2 test.

Assessment of reporting biases

We used the risk of selective outcome reporting bias from the assessment tool to assess selective or incomplete reporting (see Assessment of risk of bias in included studies). We did not construct funnel plots or tests for asymmetry for assessment of publication bias, since there were fewer than 10 trials included in each of the meta-analyses (Higgins 2017).

Data synthesis

We pooled data using a random-effects model in Review Man Web (Review Manager Web). If there were fewer than three trials in a comparison, we used a fixed-effect model. If there was inconsistency between individual study results, such that a pooled result may not be a good summary of the individual trial results (e.g. the effects were in different directions, or $I^2 > 50\%$ and corresponding $P \leq 0.10$), we did not pool the data, but described the (pattern of) individual study results. If there was statistical heterogeneity but all the effect estimates were in the same direction, such that a pooled estimate would seem to provide a good summary of the individual trial results, we pooled the data. Pooled estimates from RCTs and NRSs were presented separately, in order to allow us to inspect for heterogeneity of the effects by study design. We did not pool data from RCTs and NRSs, as is recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2021).

Regarding included economic evaluation studies, we tabulated the characteristics and results of these studies, supplemented by a narrative summary as recommended in Chapter 20 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Shemilt 2019). We presented cost data in the currency and date as reported in the included studies, when available. In addition, we converted measures of costs to 2017 USD, using the PPP for GDP as described in the Primary outcomes section of this review. Since estimates of resource use and costs were not comparable across studies (settings), we did not present a pooled estimate (Birks 2006).

Subgroup analysis and investigation of heterogeneity

We could not identify sufficient trials and studies for comparison of the effect of treatment for ISBCS compared to DSBCS in the following subgroups.

- Selected participant populations that undergo ISBCS (e.g. medical reason for ISBCS).
- Participants with and without ocular comorbidity.
- High-income countries versus low- and middle-income countries (LMICs).

Sensitivity analysis

We could not perform the planned sensitivity analyses to examine the impact of the following factors: exclude high (RoB 2) and serious or critical (ROBINS-I) risk of bias (no studies left for comparison after exclusion), exclude industry-funded studies (not applicable), use change from baseline instead of final value for visual acuity (data not available).

Summary of findings and assessment of the certainty of the evidence

We prepared summary of findings tables that presented relative and absolute risks for dichotomous variables, and SMDs for continuous variables.

The outcomes included in the summary of findings tables were:

- adverse events: endophthalmitis (up to six weeks postoperatively);
- adverse events: NOT within 1.0 dioptre of target refraction (one to three months after surgery);
- adverse events: complications (up to three months after surgery);
- economic evaluation: total costs per participant;
- economic evaluation: costs per QALY;
- visual acuity (one to three months after surgery);
- PROMs: vision specific QoL (one to three months after surgery).

Two review authors (LSS and RWPS) independently graded the overall certainty of the evidence for each outcome using the GRADE classification and GRADEpro GDT software (GRADEpro GDT). The overall RoB 2 judgement was used to feed into the GRADE assessment. We followed the recommendations provided by Schünemann regarding the use of NRSs in the summary of findings table (Schünemann 2013).

RESULTS

Description of studies

Results of the search

One search identified RCTs and NRSs and a separate search identified reports of economic studies.

The RCTs and NRS search identified 1893 records. After removal of 699 duplicates, there were 1194 records for assessment. After screening, we assessed 66 full-text articles for eligibility according to the criteria specified in the protocol (Dickman 2019). We identified 16 reports of 14 studies meeting the inclusion criteria for this review. Three reports of two ongoing studies meet the inclusion criteria and will be assessed when data become available (NCT01841957; NCT03400124). A total of 14 full-text studies were included in the review for qualitative syntheses. Nine studies were included in the quantitative syntheses: two RCTs and seven NRSs. The remaining studies were economic evaluations. Results of these studies were tabulated and not included in a meta-analysis, since results could not be pooled. The flowchart of the process of selection of studies, as well as reasons for exclusions, are presented in Figure 1.

Figure 1. Study flow diagram (PRISMA).

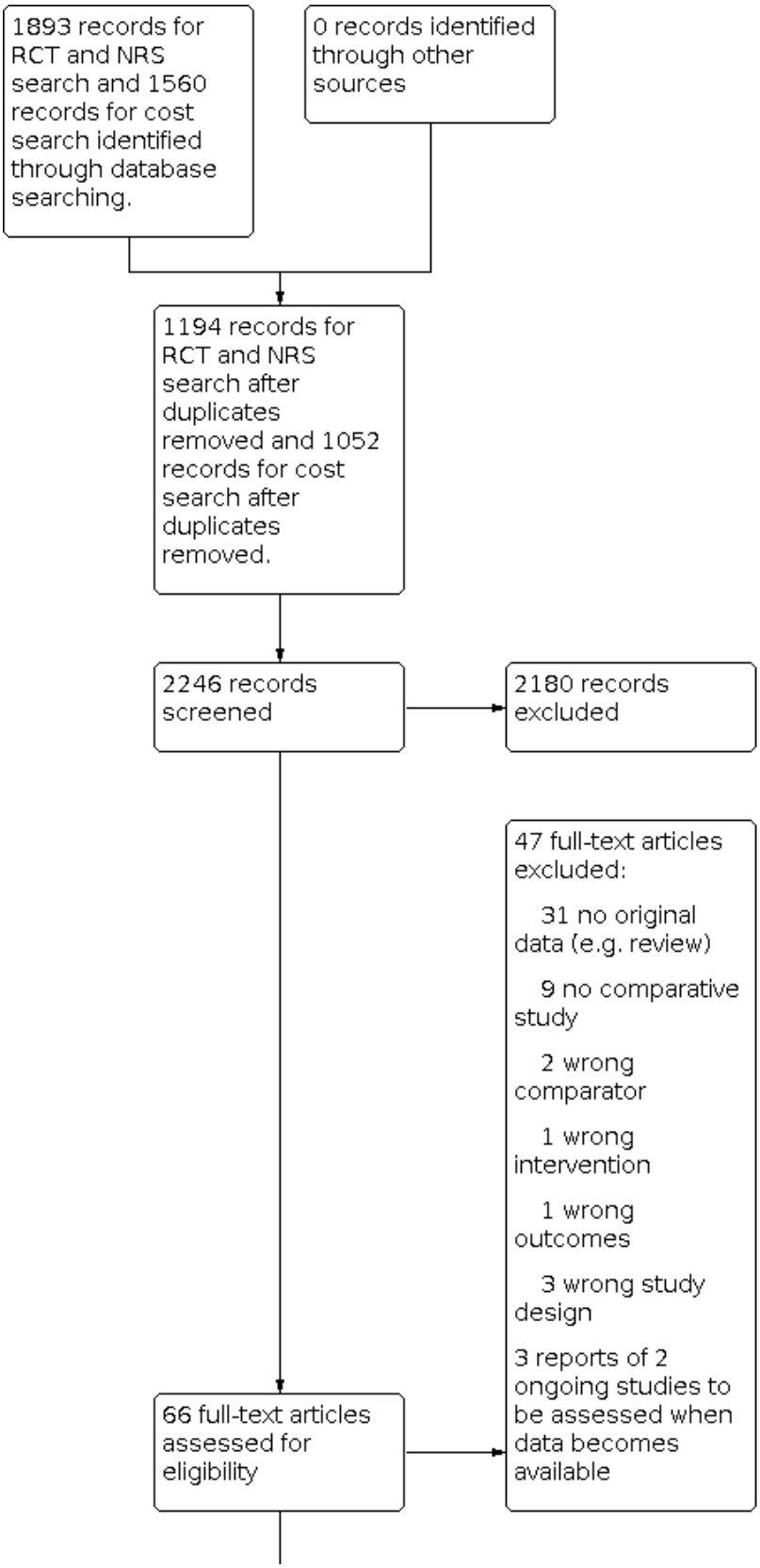
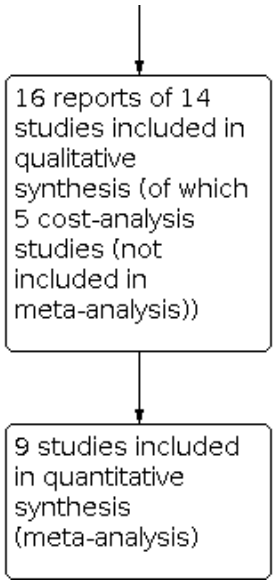


Figure 1. (Continued)



The economic searches yielded 1560 studies and, after removal of 508 duplicates, there were 1052 records for assessment. After screening, none of the included references from the economic database searches were eligible for full-text assessment. Consequently, economic studies included in this review were derived from the search for RCTs and NRSs.

Included studies

The included studies consisted of two RCTs, seven NRSs, and six cost-evaluations (one study was an NRS and cost-analysis), with 276,260 participants (7384 for ISBCS and 268,876 for DSBCS). Details of the individual studies that were included in this review are summarised in Table 1. Additional information on each of the individual trials is presented in the Characteristics of included studies table.

Table 1. Details of studies included in the review

Study	Country	Design	Eyes reported	Total number of participants	Number of participants	
					ISBCS	DSBCS
Buchan 2020	UK	Retrospective cohort study (NRS)	Both eyes	249,414	1073	248,341
Cholevik 2015	Czech Republic	Retrospective cohort study (NRS)	Both eyes	100	50	50
Chung 2009	South Korea	NRS	Both eyes	194	94	100
Herrinton 2017	USA	Retrospective cohort study (NRS)	Both eyes	24,615	5247	19,368
Kim 2015	Korea	Retrospective cohort study (NRS)	Both eyes	140	70	70
Leivo 2011	Finland	RCT-based CA Based on RCT from Sarikkola 2011	Both eyes	520 (241 included in non-health-care and time-CA)	Unclear	Unclear
Lundstrom 2009	Sweden	Model-based CA	Both eyes	97	17	80

Malvankar-Mehta 2013	Canada	Model-based CA; decision tree model	NA	NA	NA	NA
Nassiri 2009	Iran	NRS	Both eyes	220	80	140
Neel 2014a	USA	Model-based CA	NA	NA	NA	NA
O'Brien 2010	Canada	NRS-based CA	NA	44	22	22
Rush 2015	USA	Prospective NRS-based CA (NRS and CA)	Both eyes	84	42	42
Sarikkola 2011	Finland	RCT	Both eyes	507	250 (247 underwent surgery)	257 (255 underwent surgery)
Serrano-Aguilar 2012	Spain, Canary Islands	RCT	Both eyes	845	439 (417 underwent surgery)	406 (390 underwent surgery)

CA: cost analysis; DSBCS: delayed sequential bilateral cataract surgery; ISBCS: immediate sequential bilateral cataract surgery; NA: not available/applicable; NRS: non-randomised study; RCT: randomised controlled trial.

Participants and interventions

Table 2 shows mean age and the percentage of men enrolled in the study and presents the period between both surgeries for people with DSBCS. In addition, we listed whether ISBCS was performed according to advised principles (Arshinoff 2012) and antibiotic use. Inclusion and exclusion criteria for participants are presented in the Characteristics of included studies table. Most studies excluded people at increased risk of complications during surgery. Other commonly applied exclusion criteria were conditions that increased the risk of endophthalmitis and ocular conditions with an impact on (postoperative) visual acuity. Only two studies accounted for potential ocular biometry influences such as axial length (Nassiri 2009; Sarikkola 2011).

Table 2. Details of participants and interventions of included studies

Study	Mean age (SD), years		Male, %		Period between surgeries for DSBCS	ISBCS according to principles	Antibiotics used
	ISBCS	DSBCS	ISBCS	DSBCS			
Buchan 2020	71.5 (14.4)	75.6 (9.7)	37.5	40	Within 1 year of first eye (44.4% within 3 months, 84.5% within 6 months)	NR	NR
Cholevik 2015	72.2 (6.8)	74.0 (6.2)	36	42	NR	Yes, although unclear whether separate batches/sterilisation cycles were used	Topical antibiotic + intracameral cefuroxime
Chung 2009	66.4 (9.4)	65.3 (11.1)	41.5	42	2 days	Yes, although not clear whether separate batches/sterilisation cycles were used	Topical antibiotic + subconjunctival tobramycin
Herrinton 2017	NR	NR	39	38	Within 1 year of first eye	NR	Intracameral antibiotic from 2013 onwards
Kim 2015	71.2 (6.9)	70.3 (8.6)	NR	NR	1–2 months	NR	2010–2013 topical antibiotic, 2014 onwards intracameral moxifloxacin
Leivo 2011	NR	NR	NR	NR	4–6 weeks	Yes	Topical antibiotic + intracameral cefuroxime
Lundstrom 2009	NR for groups separately, for total study population: 77.9 (9.0)	NR for groups separately, for total study population: 77.9 (9.0)	NR for groups separately, for total study population: 28	NR for groups separately, for total study population: 28	5.5 months (SD 4.6)	NA	NA
Malvankar-Mehta 2013	NA	NA	NA	NA	NA	NA	NA
Nassiri 2009	67.3 (7.2)	66.6 (5.6)	45	46.4	2 months	Yes, although unclear whether separate batch-	Topical antibiotic + intracameral vancomycin

						es/ sterilisation cycles were used	
Neel 2014a	NA	NA	NA	NA	NA	NA	NA
O'Brien 2010	NR	NR	NR	NR	NR	NR	NR
Rush 2015	66.3 (NR)	65.9 (NR)	57.1	50	1–3 weeks	Yes	Topical antibiotic + intracameral vancomycin
Sarikkola 2011	75.3 (7.9)	75.0 (8.1)	26.4	25.7	4–6 weeks	Yes	Topical antibiotic + intracameral cefuroxime
Serra-no-Aguilar 2012	72.9 (8.2)	71.7 (7.9)	38.8	39.5	6 weeks	Yes, although not clear whether separate batch-es/ sterilisation cycles were used	Topical antibiotic + intracamer-al cefuroxime/vancomycin in bal-anced salt solution

DSBCS: delayed sequential bilateral cataract surgery; ISBCS: immediate sequential bilateral cataract surgery; NA: not available/applicable; NR: not reported; SD: standard deviation.

Excluded studies

We excluded 47 studies (see Characteristics of excluded studies table for their reasons for exclusion).

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

There are two ongoing studies (see Characteristics of ongoing studies table).

Risk of bias in included studies

Risk of bias in included randomised controlled trials and non-randomised studies

For RCTs, overall risk of bias was graded 'high to some concerns' for complications, 'some concerns' for refractive outcomes and visual acuity, and 'high' for PROMs. Overall risk of bias for NRSs was graded 'serious' regarding complications and 'serious to critical' regarding refractive outcomes. An overview of risk of bias judgements for each outcome is provided per study in Figure 2; Figure 3; Figure 4; Figure 5; Figure 6; Figure 7; Figure 8, at the side of forest plots for RCTs, and in additional tables: Table 1; Table 2; Table 3; Table 4; Table 5; and Table 6.

Figure 2. RoB 2 assessment for ISBCS versus DSBCS in people with bilateral age-related cataracts: complications up to three months after surgery (effect of assignment).

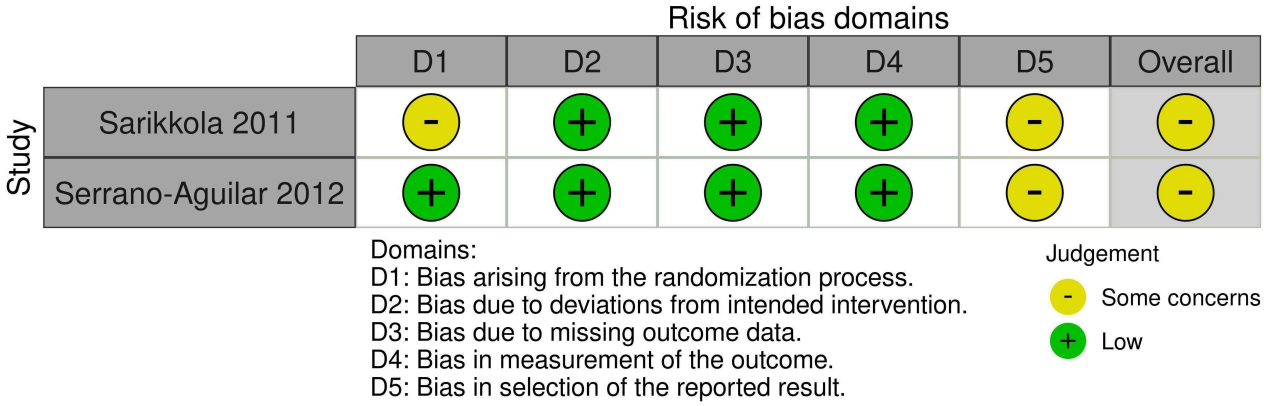


Figure 3. RoB 2 assessment for ISBCS versus DSBCS in people with bilateral age-related cataracts: complications up to three months after surgery (effect of adherence).

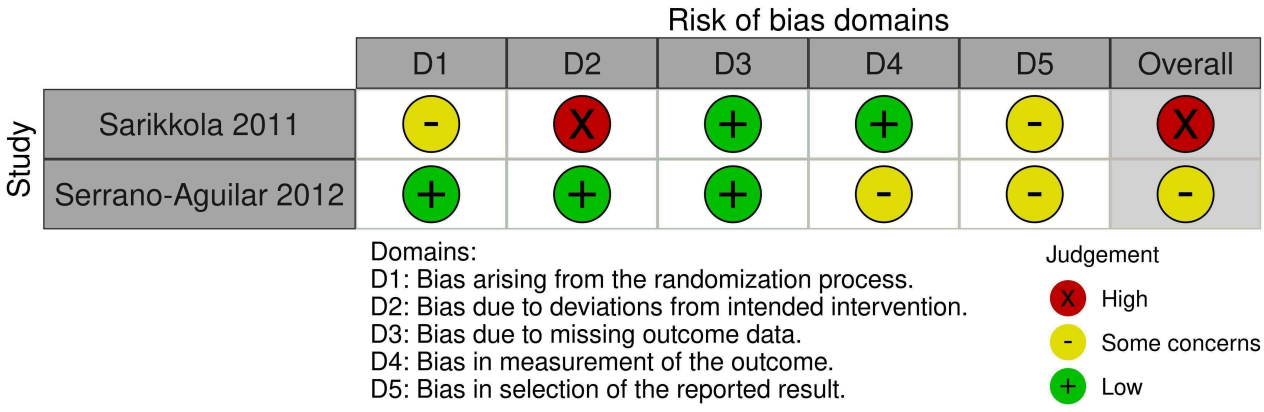


Figure 4. RoB 2 assessment for ISBCS versus DSBCS in people with bilateral age-related cataracts: refraction at one to three months after surgery (effect of assignment).

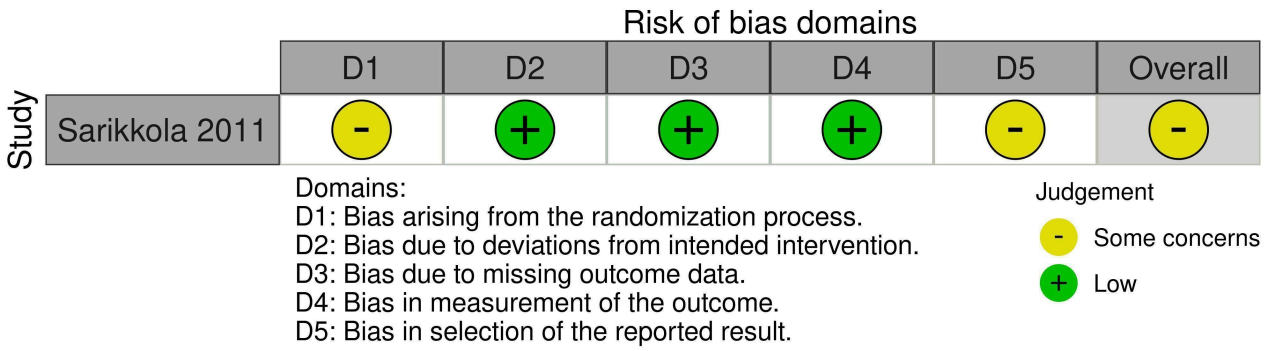


Figure 5. RoB 2 assessment for ISBCS versus DSBCS in people with bilateral age-related cataracts: best-corrected distance visual acuity (BCDVA) (effect of assignment).

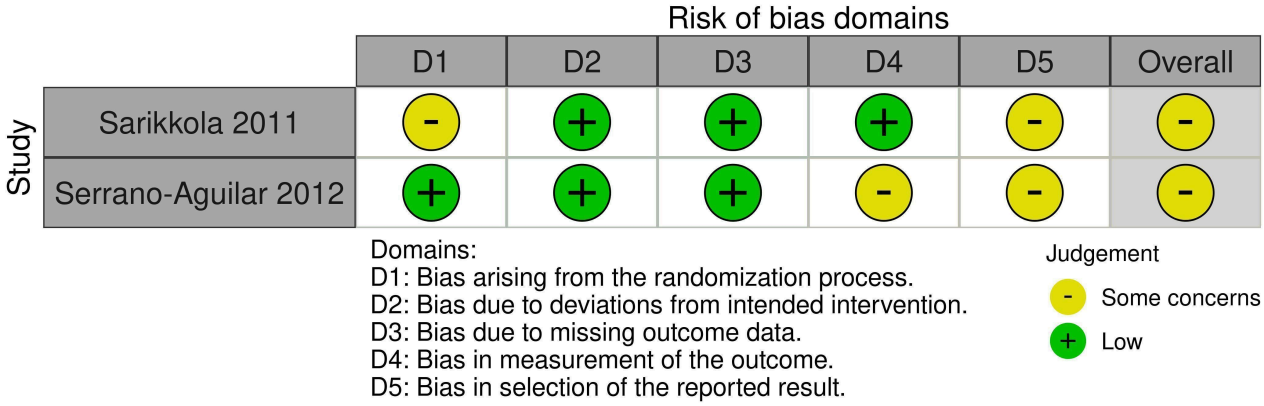


Figure 6. RoB 2 assessment for ISBCS versus DSBCS in people with bilateral age-related cataracts: patient-reported outcome measures (PROMs) up to three months after surgery (effect of assignment).

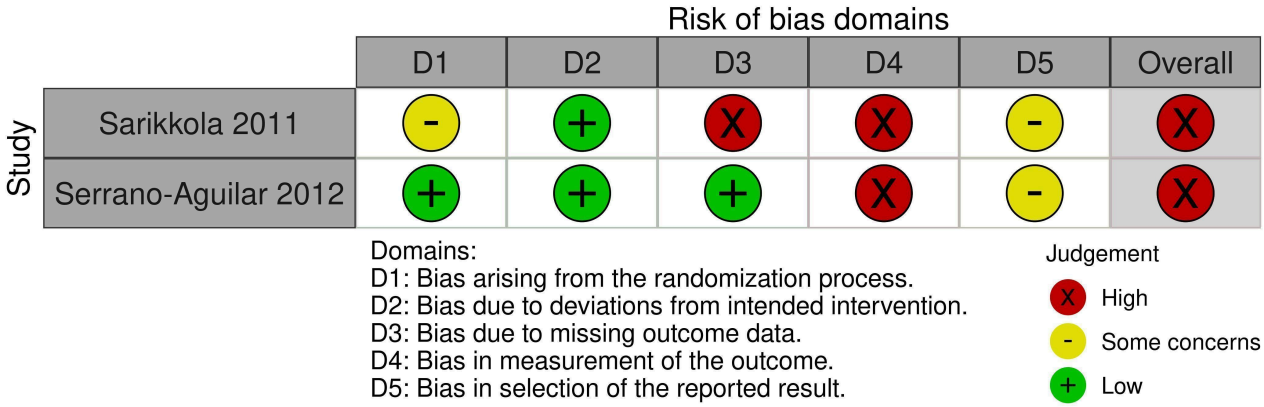


Figure 7. ROBINS-I assessment for ISBCS versus DSBCS in people with bilateral age-related cataracts: complications (endophthalmitis, intraoperative, postoperative) up to three months after surgery (effect of assignment).

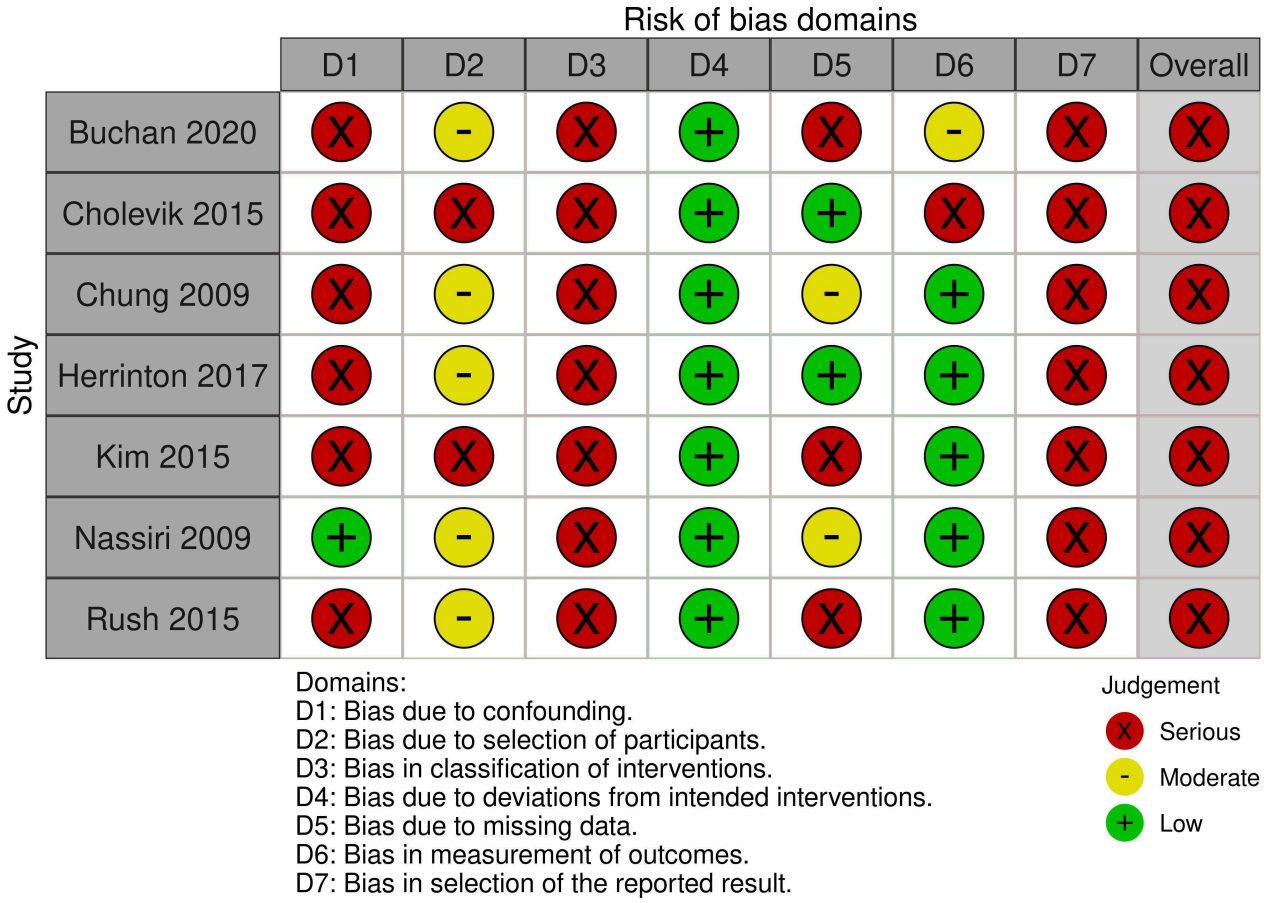
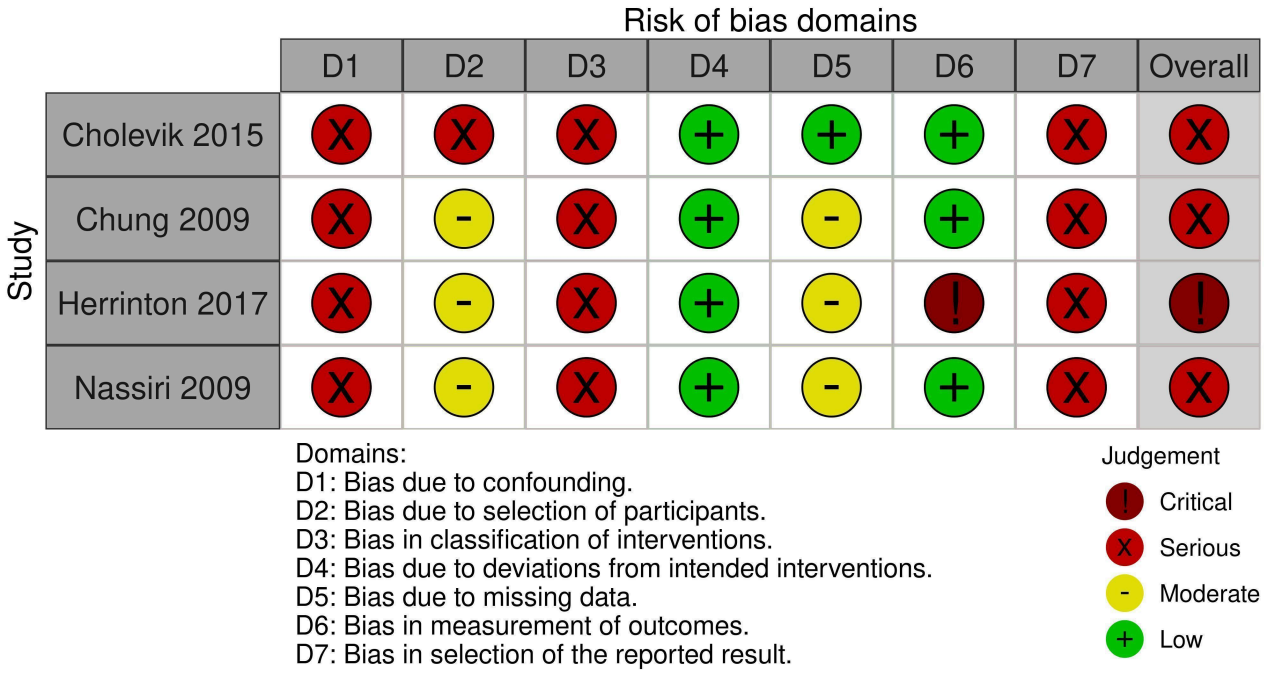


Figure 8. ROBINS-I assessment for ISBCS versus DSBCS in people with bilateral age-related cataracts: refraction at one to three months after surgery (effect of assignment).



Summary of risk of bias for key outcomes of this review

For RCTs, the risk of bias for complications (i.e. endophthalmitis, intraoperative or postoperative complication) was 'some concerns' for the effect of assignment and 'some concerns' to 'high' for the effect of adherence. For the effect of assignment, this was mainly because authors reported poorly on predefined protocols or statistical analysis plans for reporting of the results. Regarding the effect of adherence, this was mainly because of deviations from the intended interventions, since the RCT of Sarikkola 2011 reported that some participants in the study group had surgery on a separate day because of surgeon preference. This could be a result of complications in the first eye, thereby influencing the outcomes, but study authors reported no analysis to estimate the effect of adhering to the intervention.

For NRSs, risk of bias for complications was 'serious' across all studies, because of serious potential of confounding and risk of immortal time bias (e.g. ISBCS-treated participants experiencing complications during first eye surgery defined as DSBCS-treated participants instead). Additionally, study authors reported poorly on predefined protocols or statistical analysis plans for reporting of the results.

Regarding refractive outcomes, the risk of bias for the one RCT was 'some concerns', mainly because the randomisation process and predefined protocols or statistical analysis plans for reporting of the results were described in insufficient detail.

For NRSs, the risk of bias was 'serious' for most included studies, for the same reasons described for risk of bias for complications. In addition, for one NRS, the risk of bias was 'critical' since the measurement of the outcome 'refraction' had a potentially very high impact on the true outcomes for refractive surprise (Herrinton 2017): there were no data on preoperative refractive target and refractive error was measured using emmetropia as a target for all participants, excluding cases that deviated from emmetropia greater than 2 dioptres.

Risk of bias arising from the randomisation process (randomised controlled trials)

Two RCTs reported the outcomes: complications, BCDVA, and PROMs (Sarikkola 2011; Serrano-Aguilar 2012). Sarikkola 2011 was the only RCT to report refractive outcomes. We rated Sarikkola 2011 at 'some concerns' regarding risk of bias for the domain 'randomisation process', since randomisation was achieved using sealed envelopes, but no further information on the process (e.g. numbering of the envelopes, procedure for sealing) was provided. Serrano-Aguilar 2012 used a computer-generated randomisation sequence for participant allocation that was supervised by an SECSC researcher (i.e. a health service researcher from the Health Technology Assessment Unit, Government of the Canary Islands, Spain) to ensure integrity. Therefore, we graded this study at low risk of bias.

Risk of bias due to confounding (non-randomised studies)

Seven NRSs reported on complications of ISBCS compared to DSBCS. Only Nassiri 2009 was graded at low risk of bias due

to confounding, since this study listed important confounders for increased risk of complications as exclusion criteria. All other studies were graded as serious risk of bias, since not all potential confounders (e.g. ocular comorbidities, risk factors for endophthalmitis or complications) were controlled for, or because potential confounders were not balanced at baseline between groups.

All four studies that reported on refractive outcomes were graded at serious risk of bias (Cholevik 2015; Chung 2009; Herrinton 2017; Nassiri 2009). None of these studies reported on differences in baseline characteristics for potential confounders such as biometry measurements (e.g. axial length).

Bias in classification of interventions (non-randomised studies)

All seven NRSs were at risk of immortal time bias and were, therefore, graded at serious risk of bias for this domain, since the definition of the intervention may rely on events occurring after inclusion and assignment to a treatment group (e.g. ISBCS-treated participants experiencing complications during first eye surgery defined as DSBCS-treated participants instead). In NRSs, the DSBCS group is likely to consist of both 'elective' DSBCS-treated participants and 'situational' DSBCS-treated participants who were initially scheduled for ISBCS but had second eye deferred. Details on these separate categories should be presented to reduce the risk of bias regarding classification of interventions. In Cholevik 2015, two participants who were initially planned for ISBCS were placed in the DSBCS group after postponing the option for the second eye. Since postponement was due to complications, this could favour the outcomes for the ISBCS group. Herrinton 2017 reported 25 participants (0.7%) initially planned for ISBCS were converted to DSBCS after the occurrence of complications.

Bias in selection of participants into the study (non-randomised studies)

Four NRSs were retrospective (Buchan 2020; Cholevik 2015; Herrinton 2017; Kim 2015). Therefore, it was not possible to determine whether participant selection was free of bias. Both intervention and outcome could be related to the selection process. Hence, we graded these studies at moderate to serious risk of bias.

The remaining three NRSs were prospective. In Chung 2009, additional exclusion of participants took place based on participant characteristics observed *after* allocation to the intervention (i.e. ocular comorbidities). However, exclusion numbers were comparable between groups. Therefore, we graded this study at moderate risk of bias. We also graded Nassiri 2009 and Rush 2015 at moderate risk of bias for participant selection. In both studies, important risk factors that could influence selection were accounted for in the exclusion criteria. However, some possible risk factors that could influence selection into the study (e.g. biometry parameters such as anterior chamber depth) were not reported. Still, this could be related to the choice of intervention regarding the reported outcomes (complication, refraction).

Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) (randomised controlled trials and non-randomised studies)

Both included RCTs were at low risk for this type of bias. Masking was not possible due to the nature of the study. In Sarikkola 2011, some participants in both study groups had second-eye surgery deferred or cancelled, which would also happen outside the trial context. No deviations were reported that were presumably related to the trial context and it was unlikely that the outcomes were affected. In Serrano-Aguilar 2012, all participants received their allocated treatment, and an ITT analysis was performed.

Four NRSs were all undertaken in a non-experimental setting (Buchan 2020; Cholevik 2015; Herrinton 2017; Kim 2015). In Chung 2009, Nassiri 2009, and Rush 2015, participants were allocated to a group based on preference. Potential non-adherence to a certain intervention, or changes to this intervention, were most likely typical of routine care and not related to the experimental context. Therefore, these seven studies were graded at a low risk of deviation from intended intervention.

Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) (randomised controlled trials and non-randomised studies)

Sarikkola 2011 was at high risk of bias regarding complications. Some participants in the study group had surgery on a separate day because of surgeon preference. Preference for postponing second-eye surgery could be a result of complications in the first eye, thereby influencing the outcomes. No analysis to estimate the effect of adhering to the intervention was reported. Regarding other outcomes (refraction, BCDVA, and PROMs), no co-interventions were reported and the risk of bias due to effects of deviations in adherence was graded as low. In Serrano-Aguilar 2012, all participants received their allocated treatment and there were no imbalances in unplanned co-interventions. Therefore, this domain was graded at low risk of bias for this study.

Two NRSs were graded at low risk of bias, since co-interventions were the same in both groups and there were no deviations from the allocated intervention (Chung 2009; Rush 2015). Cholevik 2015, Kim 2015, and Nassiri 2009 were graded at serious risk of bias, because of non-adherence or no available information on potential differences between groups in received co-interventions or on non-adherence. For Buchan 2020, there was no information on adherence or non-adherence, and it was not reported whether there were potential (protocol) differences (e.g. use of antibiotics or administration of postoperative anti-inflammatory drugs). Finally, Herrinton 2017 was at serious risk of bias for outcomes regarding complications, since intracameral antibiotics were introduced at the start of study, while ISBCS was increasingly adopted during the study period. Therefore, it is possible that more cases of DSBCS lacked full adaptation of intracameral antibiotics, while this is less likely for ISBCS cases performed later in the study. However, regarding the effect on refractive outcomes, the risk of bias due to deviations from intended interventions was low.

Risk of bias due to missing outcome data (randomised controlled trials and non-randomised studies)

Completion of data up to one month after second-eye surgery was high for the included RCTs (96.8% completeness for Sarikkola 2011 and one participant lost to follow-up for Serrano-Aguilar 2012), and risk of bias due to missing outcome data was, therefore, low. However, completeness of data was not reported for PROMs in Sarikkola 2011. Missing data for PROMs could depend on its true value. Therefore, the risk of bias for PROMs was high for this study.

The risk of bias for this domain was serious for three NRSs, since these studies provided no information on completeness of data

or on reasons for missing data (Buchan 2020; Kim 2015; Rush 2015). Chung 2009 and Nassiri 2009 were at moderate risk of bias. In Chung 2009, cases with missing data were excluded from the analysis. However, the number of exclusions and reasons for exclusion were comparable between groups. In Nassiri 2009, data on 12.5% of ISBCS-treated participants and 18.6% of DSBCS-treated participants were missing due to lost to follow-up (reasons not provided). Cholevik 2015 and Herrinton 2017 were at low risk of bias, since data on complications were probably available for all, or nearly all, participants. Because of the nature of the outcome (complications) it is unlikely that missingness is related to the true value of the outcome (participants who experience complications were expected to return to the hospital). In Cholevik 2015, data on refractive outcomes were available for at least 91% (low risk) of participants. Since completeness regarding refractive outcomes was estimated at about 65% for Herrinton 2017, we graded this study at moderate risk of bias for this outcome.

Risk of bias in measurement of the outcome (randomised controlled trials and non-randomised studies)

Both RCTs were at low risk of bias for this domain, except for PROMs (Sarikkola 2011; Serrano-Aguilar 2012). Since participants were aware of the intervention received and PROMs are a subjective measurement that could be influenced by knowledge of treatment allocation. Therefore, we graded these studies at high risk of bias for PROMs.

Regarding NRSs, all studies were graded at low risk of bias for this domain, except for Buchan 2020 (outcome: complications), Cholevik 2015 (outcome: complications), and Herrinton 2017 (outcome: refraction). Buchan 2020 provided information on the methods for measurement of the outcome, though assessment of (severe) complications was less likely to have been influenced by knowledge of the intervention due to the nature of the outcome. For Cholevik 2015, it was unclear how data collection was performed. Since ISBCS-treated participants had at least one additional follow-up examination compared to DSBCS-treated participants, an extra opportunity for identifying adverse events was created for ISBCS-treated participants. Therefore, the risk of bias for this study was serious. For Herrinton 2017, there were no data on preoperative refractive target and refractive error was measured using emmetropia as a target for all participants, excluding cases that deviated from emmetropia greater than 2 dioptres. Since this has a potentially high impact on true outcomes regarding refractive surprise, we graded this domain at critical risk of bias regarding refractive outcomes.

Risk of bias in selection of the reported result (randomised controlled trials and non-randomised studies)

There were no trial protocol or statistical analysis plans regarding analysis intentions for all included studies. Following the RoB 2 and ROBINS-I tools, this domain was graded at 'some concerns' regarding risk of bias for RCTs and at serious risk of bias for NRSs.

Risk of bias in economic evaluations

For economic evaluations, the risk of bias measured by the CHEC-list, the NICE-checklist and the CHEERS-checklist, are presented in additional Table 1; Table 2; and Table 3, respectively. In addition to these checklists, we used the RoB 2 or ROBINS-I tool to assess risk of bias for trial-based economic evaluations (Leivo 2011; Rush 2015). Rush 2015 was at high risk of bias and Leivo 2011 (based on the trial of Sarikkola 2011), was at high to moderate risk of bias. Details of these assessments can be found in the 'Risk of bias in included randomised controlled trials and non-randomised studies' section above. In O'Brien 2010, the characteristics, methods, and results of the non-randomised trial part of the study were not described in detail. Therefore, assessment of risk of bias using the ROBINS-I tool was not possible for this study. Evaluation of this study using the CHEERS-checklist showed lack of description of important items, such as target population and subgroups, currency and conversion of costs, study parameters, and sources of funding. Furthermore, 11/19 items of the CHEC-list were not addressed appropriately.

Of the model-based economic evaluations, one study was considered to be of critical risk of bias (Malvankar-Mehta 2013). Reasons for this assessment were mainly that QALYs were not measured using preferred methods and that errors were made in the calculation of costs: Malvankar-Mehta 2013 was a model-based cost-utility analysis using data from previous studies inputted into the model. The hospital costs were derived from O'Brien 2010. They reported that the total hospital costs were CAN 1059.1 for ISBCS and CAN 1566.3 for DSBCS. These are the full hospital costs for both eyes. Malvankar-Mehta 2013 correctly used CAN 1059.1 as the total hospital costs for ISBCS, but erroneously counted the hospital costs for DSBCS twice (i.e. CAN 3132.6 instead of CAN 1566.3), leading to a gross overestimation of the costs of DSBCS. The utilities used by Malvankar-Mehta 2013 were sourced from the study of Brown 2001, in which QoL was measured using acceptable methods: time trade-off (TTO) and standard gamble (SG). However, Brown 2001 measured QoL in one group of participants with two 'good' eyes and one group of participants with only one 'good' eye (with a visual acuity in the other eye of less than 0.5). Mean QoL was 0.97 for the group of participants with two 'good' eyes and 0.89 for participants with only one 'good' eye. Malvankar-Mehta 2013 used a utility value of 0.97 for ISBCS-treated participants with successful surgery in both eyes. Meanwhile, a utility value of 0.89 was used for all DSBCS-treated participants with successful surgery in both eyes as well as in all participants in which second-eye surgery was deferred. Thereby, it is unfairly assumed that all DSBCS-treated participants with uncomplicated unilateral or bilateral surgery have a QoL equal to participants with only one eye with good vision. In addition, discounting was not applied in a correct manner (Drummond 2015; Hakkaart-van Roijen 2015). Other included model-based cost analyses were graded to have potentially serious limitations (Lundstrom 2009; Neel 2014a). For Lundstrom 2009, this was due to a lack of description of the time horizon and since the impact and costs of postoperative complications were not included in the model. Furthermore, not all relevant costs from a healthcare or societal perspective (e.g. productivity losses, home care) were included for the short-term postoperative period and estimates of resource use were derived from a single study. As for Neel 2014a, costs were largely based on reimbursement prices, the time horizon was limited to the day of surgery, no effectiveness parameters were included in the analysis, and estimates of resource use were derived from a single centre.

Effects of interventions

See: **Summary of findings 1** ISBCS compared to DSBCS in people with bilateral age-related cataracts (RCTs); **Summary of findings 2** ISBCS compared to DSBCS in people with bilateral age-related cataracts (NRSs)

The overview of the included studies reporting on each of the outcomes defined for this review is presented in Table 3. Data on BCDVA and PROMs were collected only for RCTs. Data on safety (endophthalmitis, refraction, and other complications) were collected for both RCTs and NRSs. In addition, we performed meta-analyses for the outcomes: endophthalmitis, refraction 0.5 and 1.0 dioptre of target, intraoperative and postoperative complications, and PROMs. In the meta-analyses, we presented pooled estimates for RCTs and NRSs separately. For BCDVA and costs, results could not be pooled since data were too heterogeneous to allow comparison. Therefore, results were tabulated and presented narratively. In addition, since the included studies used multiple ways of presenting results on BCDVA (mean with range versus proportions of participants with a certain BCDVA or better), tabulating the reported results on BCDVA prevented selective outcome reporting for this outcome.

Since none of the outcomes included 10 or more trials in a meta-analysis, we did not construct funnel plots to test for asymmetry for assessment of publication bias (Higgins 2017). Since data were available for all eyes but not for first and second eyes separately for almost all included studies, we could not adjust for within-person correlation. Only one study reported intraoperative and postoperative complications for second eyes separately (Sarikkola 2011). Therefore, these results are not pooled but are described instead under 'intraoperative and postoperative complications' below.

If possible and if applicable, we contacted the authors for additional data. However, we received no additional data. Hence, all data presented in the review were obtained from published sources. For the included RCTs, ITT data were available and used in the analyses, and the amount of missing data was low. For NRSs, the risk of bias due to missing outcome data ranged from low to serious (see 'Risk of bias due to missing outcome data (randomised controlled trials and non-randomised studies)' section), and, in the absence of ITT data, we used available-case data, assuming data were missing completely at random. Some included studies reported reasons and comparable percentages for missing data between groups. Additionally, missing data were unlikely to be related to the true value of the outcome due to the nature of the outcomes derived from NRSs (complications). However, it should be noted that some studies did not report or explain missing data.

Although we set out to evaluate the effect of assignment and adherence, the included studies either did not provide data on adherence or all included participants adhered to the assigned intervention (i.e. no deviation from protocol). Therefore, we could not include analyses on adherence in the current review. This applied to all outcomes, except for data on endophthalmitis from RCTs. In this analysis, ITT data differed from PP data for the study of Sarikkola 2011, but not for the study of Serrano-Aguilar 2012. However, since there were no cases of endophthalmitis in either study, no relative effects could be estimated.

Furthermore, we planned to check the skewness of data for the continuous outcomes of this review (cost, visual acuity, and PROMs). For costs, there were no distribution data and skewness could not be checked. With regard to visual acuity, we evaluated reported means and ranges to evaluate the possibility of skewed data. Based on these parameters, it was unclear whether skewness of data was an issue for the baseline visual acuity reported by Sarikkola 2011. For the data reported by Serrano-Aguilar 2012, baseline visual acuity data were likely positively skewed, whereas postoperative data was likely to be negatively skewed (see section on secondary outcomes). With regard to PROMs, we could not check for skewness, because only mean and SDs were reported. Since the outcome (change in PROMs from baseline to three months' follow-up) could be zero or negative, we could not use the recommendations of Altman 1996 to check for skewness.

The main findings are summarised in the Summary of main results section of this review. In addition, the effects of the interventions are summarised for RCTs (see Summary of findings 1) and NRSs (see Summary of findings 2), and pooled estimates are presented in the comment boxes.

Table 3. Outcomes for this review per included study – randomised controlled trials and non-randomised studies

Study	Outcomes														
	Endophthalmitis	Refraction < 0.5 of target		Refraction < 1.0 of target		Intraoperative complications	Postoperative complications	BCVA			PROMS				
		1 week	1–3 months	1 week	1–3 months			Baseline	1 week	1–3 months	Baseline	1 week	1–3 months	Change baseline to 1 week	Change baseline to 1–3 months
Sarikkola 2011 (RCT)	x	NR	x	NR	x	x[a]	x[a]	x	NR	x	x	NR	NR	NR	x
Serrano-Aguilar 2012 (RCT)	x	NR	NR	NR	NR	x	x	x	NR	x	x	NR	x	NR	x
Buchan 2020 (NRS)	x	NR	NR	NR	NR	x	NR	NA	NA	NA	NA	NA	NA	NA	NA
Cholevik 2015 (NRS)	x	NR	x	NR	x	x	x	NA	NA	NA	NA	NA	NA	NA	NA
Chung 2009 (NRS)	x	NR	x	NR	x	x	x	NA	NA	NA	NA	NA	NA	NA	NA
Herrinton 2017 (NRS)	x	NR	NR	NR	NR	x	x	NA	NA	NA	NA	NA	NA	NA	NA
Kim 2015 (NRS)	x	NR	NR	NR	NR	NR	NR	NA	NA	NA	NA	NA	NA	NA	NA
Nassiri 2009 (NRS)	x	NR	NR	NR	x	x	x	NA	NA	NA	NA	NA	NA	NA	NA
Rush 2015 (NRS)	x	NR	NR	NR	NR	x	x	NA	NA	NA	NA	NA	NA	NA	NA

NA: not applicable (reason: this outcome is only included for RCTs); NR: not reported; NRS: non-randomised study; RCT: randomised controlled trial.

[a]Also reported for second eyes separately.

Primary outcomes

Endophthalmitis

Nine studies (ISBCS: 7701 participants/15,402 eyes; DSBCS: 278,765 participants/557,530 eyes) reported the occurrence of endophthalmitis (Buchan 2020; Cholevik 2015; Chung 2009; Herrinton 2017; Kim 2015; Nassiri 2009; Rush 2015; Sarikkola 2011; Serrano-Aguilar 2012) (Analysis 1.1). None of the studies reported any cases of bilateral endophthalmitis. Only the NRS of Herrinton 2017 was large enough to identify this event occurring unilaterally at least once in both groups. In Buchan 2020, the DSBCS treatment arm was large enough to identify multiple unilateral endophthalmitis cases, though this was not the case for the ISBCS treatment arm. All other studies report no cases of endophthalmitis. However, in Buchan 2020 and Herrinton 2017, there was no information on the severity of endophthalmitis, whether endophthalmitis cases were confirmed by microbiological investigation of aqueous or vitreous samples, or on the course of the disease during follow-up.

With regard to RCTs, two studies (2610 participants) recorded no events and thus relative effect measures could not be estimated for this outcome (Analysis 1.1; Analysis 1.2). For NRSs, two studies provided relative effect estimates reporting on 12,640 ISBCS eyes (one event) and 535,418 DSBCS eyes (55 events) (RR 1.97, 95% CI 0.32 to 12.16; Analysis 1.3) (Buchan 2020; Herrinton 2017). The five other NRSs (1436 ISBCS eyes and 20,828 DSBCS eyes) recorded no events. Furthermore, to perform a GRADE assessment on the imprecision for this outcome, we used the corresponding absolute risk with ISBCS as calculated by GRADEpro Summary of findings 2. This resulted in an absolute risk with ISBCS of 0.019% (95% CI 0.003 to 0.12%). There was no substantial inconsistency between studies (I^2 = 0%).

The certainty of the evidence for endophthalmitis was low for RCTs, due to downgrading two levels for imprecision, as sample sizes and number of events (zero) were too small to adequately measure the outcome and estimate the effect. For NRSs, the certainty of the evidence was low, due to downgrading one level because of serious risk of bias and one level for imprecision of the evidence, since the absolute risk of 0.019% (95% CI 0.003 to 0.12%) for ISBCS, could not exclude important benefit or harm (the upper CI of 0.12% is higher than currently reported rates for unilateral endophthalmitis (Grzybowski 2021a). We did not use the CI of the relative effect for grading of imprecision because of the more informative value of the absolute effect in the case of extremely rare events (Guyatt 2011).

Refraction

Regarding refractive outcomes, none of the included studies reported the percentage of eyes outside 1.0 dioptre or 0.5 dioptre of target one week after surgery. Three studies reported the percentage of eyes NOT within 0.5 dioptre of target one to three months after surgery (ISBCS: 385 participants/770 eyes; DSBCS: 395 participants/790 eyes) (Analysis 1.4; Analysis 1.5) (Cholevik 2015; Chung 2009; Sarikkola 2011). Four studies (ISBCS: 455 participants/910 eyes; DSBCS: 509 participants/1018 eyes) reported the percentage of eyes NOT within 1.0 dioptre of target one to three months after surgery (Analysis 1.6; Analysis 1.7) (Cholevik 2015; Chung 2009; Nassiri 2009; Sarikkola 2011). Although the study of Herrinton 2017 did report on refractive outcomes, the results of this study could not be included in this review. This was because reported percentages were calculated for within 0.5 dioptre from emmetropia, rather than for 0.5 dioptre within target refraction of the individual participant (see Risk of bias in included studies section). Furthermore, Kim 2015 reported refractive outcomes, but not on the percentages of eyes that did or did not fall within target. Therefore, refractive outcomes could not be included for this study. Overall, it should be noted that none of the studies provided information on the protocol for adjustment of the IOL power in the second eye based on refractive outcomes of the first eye in DSBCS-treated participants.

For RCTs, there was only one study regarding refractive outcomes NOT within 0.5 dioptres of target one to three months after surgery. This study found an RR of 1.07 (95% CI 0.89 to 1.28; Analysis 1.4). With respect to NRSs, the RR was 1.24 (95% CI 0.84 to 1.83; Analysis 1.5). Although there was some inconsistency between NRSs (I^2 = 56%), it was not significant (P = 0.13). Regarding refractive outcomes NOT within 1.0 dioptre of target, the RCT showed an RR of 0.84 (95% CI 0.57 to 1.26; Analysis 1.6). For NRSs, the pooled RR was 1.02 (95% CI 0.60 to 1.75; Analysis 1.7), with no inconsistency between studies (I^2 = 0%).

The certainty of the evidence on refractive outcomes was moderate for RCTs and low for NRSs. For both RCTs and NRSs, we downgraded one level for imprecision since the CI of the effect failed to exclude important benefit or harm. In addition, for NRSs, the evidence was downgraded one level due to serious risk of bias.

Intraoperative and postoperative complications

Seven studies reported the incidence and type of intraoperative and postoperative complications (Cholevik 2015; Chung 2009; Herrinton 2017; Nassiri 2009; Rush 2015; Sarikkola 2011; Serrano-Aguilar 2012) (Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11). Buchan 2020 reported intraoperative complications only. Regarding intraoperative complications, data were collected from 7240 ISBCS-treated participants and 268,658 DSBCS-treated participants. With respect to postoperative complications, data were collected from 6166 ISBCS-treated participants and 20,316 DSBCS-treated participants.

For intraoperative complications, we found no inconsistency between individual studies for both RCTs and NRSs (I^2 = 0%; Analysis 1.8; Analysis 1.9). The results on intraoperative complications showed a pooled RR of 0.75 (95% CI 0.47 to 1.2 1; Analysis 1.8) for RCTs and 1.13 (95% CI 0.86 to 1.48; Analysis 1.9) for NRSs.

There was inconsistency between individual studies regarding postoperative complications for both RCTs (I^2 = 65%; P = 0.09; Analysis 1.10) and NRSs (I^2 = 78%; P = 0.001; Analysis 1.11). This is most likely due to a difference between studies in definition of complications. The pooled RR was 1.33 (95% CI 0.52 to 3.40; Analysis 1.10) for RCTs and 1.04 (95% CI 0.47 to 2.29; Analysis 1.11) for NRSs.

One study reported intraoperative and postoperative complications in second eyes only (Sarikkola 2011). The results showed no difference in intraoperative and postoperative complications between groups. Intraoperative complications occurred in 10/243 eyes (4.1%) for ISBCS and 11/246 eyes (4.5%) for DSBCS. Postoperative complications occurred in 31/243 eyes (12.8%) for ISBCS and 45/245 eyes (18.4%) for DSBCS. This relatively

high incidence of complications included anterior chamber flare and wound sutures, among others.

Regarding the certainty of the evidence on complications, the results were very low for both RCTs and NRSs. This was due to downgrading by one level for high (RCTs) and serious (NRSs) risk of bias, one level for inconsistency (because of high heterogeneity), and one level for imprecision of the results (CIs failed to exclude important benefit or harm).

Cost-effectiveness and cost-evaluations

For economic evaluations, we tabulated the results in tables 4 (study characteristics), 5 (cost outcomes), and 6 (costs converted to 2017 USD). Six studies reported the costs of ISBCS and DSBCS (Leivo 2011; Lundstrom 2009; Malvankar-Mehta 2013; Neel 2014a; O'Brien 2010; Rush 2015). Due to differences in included cost sources and time horizon employed, the results on costs could not be pooled. Only two studies reported the cost year, and we converted these to 2017 USD (Leivo 2011; Neel 2014a). These were also the only studies that reported patient, family, and societal costs. All studies reported higher mean total costs for DSBCS versus ISBCS, ranging from 14.3% (Lundstrom 2009) to 47.9% (O'Brien 2010) higher costs. Malvankar-Mehta 2013 showed that ISBCS was more cost-effective compared to DSBCS, with a short time ICER of CAD −20.082 per utility and a lifetime ICER of CAD −1431 per QALY. However, as reported in the 'Risk of bias in economic evaluations' section of this review, it should be noted that there was a gross overestimation of the costs of DSBCS, that calculated utilities assumed that all DSBCS-treated participants remained with a visual acuity of less than 0.5 in only eye for the rest of their life, and discounting was not performed correctly. In addition, the calculated ICER with QALY did not include costs over 12 years (as used for utilities). Therefore, additional costs at a later point in life (e.g. related to second eye surgery in the 20% of DSBCS that initially deferred surgery) were not taken into account.

For RCTs, the certainty of the evidence on total costs was low: we downgraded one level due to risk of bias and one level for indirectness, because results were derived from a single hospital. For NRSs, the certainty of evidence was very low: we downgraded one level due to risk of bias and one level due to differences in cost sources and time horizons employed.

Table 4. Study characteristics of included economic evaluations

Study	Currency (year)	Setting	Perspective costs	Perspective effects	Time horizon costs	Time horizon effects	Effects (utilities)	ICERs/ QALYs
Leivo 2011	EUR (2006)	Single hospital (Helsinki University Eye Hospital)	Societal	NA	3 months	NA	NA	NA
Lundstrom 2009	SEK (unclear)	Single hospital (Department of Ophthalmology, Karlskrona, Sweden)	Healthcare	NA	Unclear	NA	NA	NA
Malvankar-Mehta 2013	CAN (unclear)	Unclear	Payer	Payer	Unclear	Unclear	ISBCS: 0.96 DSBCS: 0.88	ISBCS: −20.082/utility
Neel 2014a	USD (2012)	Ambulatory surgery centre and a hospital outpatient department	Payer, patient, and societal	NA	Unclear	NA	NA	NA
O'Brien 2010	CAN (unclear)	Single hospital (London Health Sciences Centre)	Healthcare	NA	Unclear	NA	NA	NA
Rush 2015	USD (unclear)	A single private-practice ambulatory surgery centre	Payer	NA	90 (SD 14) days	NA	NA	NA

DSBCS: delayed sequential bilateral cataract surgery; ICER: incremental cost-effectiveness ratio; ISBCS: immediate sequential bilateral cataract surgery; NA: not applicable; QALY: quality-adjusted life year.

Table 5. Reported costs in included economic evaluations (in study specific currencies)

Study	Currency	ISBCS				DSBCS			
		Healthcare costs	Patient and family costs	Societal costs	Total costs	Healthcare costs	Patient and family costs	Societal costs	Total costs
Leivo 2011	EUR	2467	912	124	3503	2936	1743	234	4913
Lundstrom 2009	SEK	7929	NR	NR	7929	9059	NR	NR	9059
Malvankar-Mehta 2013	CAD	1334	NR	NR	1334	2941	NR	NR	2941
Neel 2014a	USD	2759 (ASC)/3821 (HOPD)	51	186	2996 (ASC)/4058 (HOPD)	3708 (ASC)/5124 (HOPD)	91	372	4171 (ASC)/5587 (HOPD)
O'Brien 2010	CAD	1059.10	NR	NR	1059.10	1566.30	NR	NR	1566.30
Rush 2015	USD	3123	NR	NR	3123	4067	NR	NR	4067

ASC: ambulatory surgery centre; DSBCS: delayed sequential bilateral cataract surgery; HOPD: hospital outpatient department; ISBCS: immediate sequential bilateral cataract surgery; NR: not reported.

Table 6. Costs in included economic evaluations converted to 2017 US dollars

Study	ISBCS				DSBCS			
	Healthcare costs	Patient and family costs	Societal costs	Total costs	Healthcare costs	Patient and family costs	Societal costs	Total costs
Leivo 2011	3388	1252	170	4811	4032	2394	322	6748
Lundstrom 2009	—	NR	NR	—	—	NR	NR	—
Malvankar-Mehta 2013	—	NR	NR	—	—	NR	NR	—
Neel 2014a	2944 (ASC)/4077 (HOPD)	54	198	3197 (ASC)/4330 (HOPD)	3957 (ASC)/5468 (HOPD)	97	397	4451 (ASC)/5962 (HOPD)
O'Brien 2010	—	NR	NR	—	—	NR	NR	—
Rush 2015	—	NR	NR	—	—	NR	NR	—

ASC: ambulatory surgery centre; DSBCS: delayed sequential bilateral cataract surgery; HOPD: hospital outpatient department; ISBCS: immediate sequential bilateral cataract surgery; NR: not reported.

Secondary outcomes

For visual acuity and PROMs, we included data from RCTs only (Sarikkola 2011; Serrano-Aguilar 2012).

Visual acuity

Regarding visual acuity, none of the RCTs reported BCDVA at one week after surgery. Both RCTs reported baseline values and outcomes at one to three months after surgery. Preoperative BCDVA data were available for 667 ISBCS-treated participants (1334 eyes) and 647 DSBCS-treated participants (1294 eyes). For data on BCDVA one to three months after surgery, these numbers were 661 participants (1322 eyes) for ISBCS and 637 participants (1274 eyes) for DSBCS. BCDVA results at one to three months could not be pooled, since data were too heterogeneous to allow comparison: Sarikkola 2011 reported the proportion of participants with a BCDVA of 20/25 or better, whereas Serrano-Aguilar 2012 reported the median BCDVA with range (Table 7). Both RCTs showed no evidence of a difference in BCDVA between groups one to three months after surgery. Neither RCT reported change from baseline values.

The certainty of the evidence on BCDVA was very low: we downgraded one level for inconsistency (due to a high heterogeneity), one level for indirectness of the outcome, and one level for imprecision (median with wide range was reported for the outcome).

Table 7. Visual acuity outcomes reported in included randomised controlled trials

Study	Time point	ISBCS		DSBCS		Notes
		Median (range)	Number of eyes	Median (range)	Number of eyes	
Sarikkola 2011	Baseline	20/60 (LP, 20/25)	500	20/60 (LP, 20/25)	514	All eyes
	1–3 months	NR	376/488 (77%)	NR	336/494 (68%)	Proportion of eyes (all eyes) with BCDVA 20/25 or better
Serrano-Aguilar 2012	Baseline	20/100 (LP, 20/25)	834	20/100 (LP, 20/20)	780	All eyes
	1–3 months	20/22 (LP, 20/20)	834	20/22 (LP, 20/20)	780	All eyes

BCDVA: best-corrected distance visual acuity; DSBCS: delayed sequential bilateral cataract surgery; ISBCS: immediate sequential bilateral cataract surgery; LP: light perception; NR: not reported.

Patient-reported outcome measures

Both RCTs reported PROMs. However, they used a variety of PROMs (questionnaires). Sarikkola 2011 reported Visual Function Index-7 (VF-7; a shortened version of the Visual Function Index (VF)-14), Cataract Symptom-5 score (CS-5), and trouble with vision and participant satisfaction with vision (no standardised questionnaire). Serrano-Aguilar 2012 reported the VF-14 only. Since the VF-7 and VF-14 results were derived from the same type of questionnaire (VF-7 is a shortened version of the VF-14 questionnaire), we could compare only this PROM in a meta-analysis (Analysis 1.12). Final visual function scores one to three months after surgery were available for one RCT (Serrano-Aguilar 2012) and could, therefore, not be compared in a meta-analysis. For this study, the mean (SD) results on VF-14 scores one to three months after surgery were 93.3 (SD 12.8) for ISBCS versus 95.8 (SD 8.5) for DSBCS. Both RCTs reported results on change from baseline until one to three months (ISBCS: 660 participants; DSBCS: 637 participants)(Analysis 1.12). There was no evidence of a difference in SMD for change in visual function between baseline and one to three months for ISBCS versus DSBCS (SMD −0.08, 95% CI −0.19 to 0.03). Although there was substantial inconsistency between studies (I^2 = 53%), this inconsistency was not statistically significant (P = 0.14). There was no difference in the other reported PROMS (CS-5, trouble with vision and participant satisfaction with vision) between groups.

The certainty of the evidence on PROMs was moderate: we downgraded one level due to a high risk of bias. Participants were aware of the intervention received, which is likely to have an influence on the reported outcomes.

Subgroups

With respect to all outcomes, we could not include enough studies to compare outcomes for subgroups on selected participants, ocular comorbidities, and high versus LMIC countries.

Sensitivity analysis

It was not possible to perform a sensitivity analysis by excluding studies at high (RCTs) and serious or critical (NRSs) risk of bias, since only one study would be left for comparison (Serrano-Aguilar 2012 for outcome 'complications', Sarikkola 2011 for outcome 'refraction'). Furthermore, in the protocol we described that we would compare change from baseline to one to three months for PROMs next to an analysis of the outcomes for PROMs at one to three months after surgery. However, only analysis of the change from baseline to one to three months for PROMs was performed since no data were available on the final PROMs at one to three

months. For visual acuity, no change from baseline values were available.

DISCUSSION

The aim of this review was to assess the safety, visual outcomes, and PROMs of ISBCS compared to DSBCS in people with bilateral age-related cataracts. In addition, we aimed to summarise current evidence for the incremental resource use, utilities, costs, and cost-effectiveness of ISBCS compared to DSBCS.

Summary of main results

The review included 14 studies: two RCTs, seven NRSs and six economic evaluations (one study was both an NRS and economic evaluation). These studies reported on 276,260 participants (7384 for ISBCS and 268,876 for DSBCS). A summary of the main results is presented in Summary of findings 1 and Summary of findings 2.

Regarding the primary outcomes, there was limited evidence on the risk of endophthalmitis with ISBCS compared to DSBCS. Only one NRS was large enough to identify the event occurring unilaterally at least once in both groups. Furthermore, it should be noted that in general, included numbers of ISBCS-treated participants were considerably lower than those of DSBCS-treated participants. Nonetheless, there was a very low risk of unilateral endophthalmitis in both ISBCS and DSBCS groups and none of the studies reported bilateral endophthalmitis. However, relative effects were estimated imprecisely and with low certainty, so that relative estimates were not reliable. The unilateral absolute risk with ISBCS was 0.019% (95% CI 0.003 to 0.12%). Based on descriptive evidence and partially weak statistical evidence, we found no evidence of an increased risk of endophthalmitis with ISBCS. Regarding refractive outcomes and the incidence of refractive surprise, none of the included studies reported results one week after surgery. At one to three months after surgery, we could only include refractive data from one RCT and three NRSs. We found no evidence of a difference between groups, neither was there any substantial inconsistencies between studies. As for results on intraoperative and postoperative complications (derived from two RCTs and six NRSs), there was no evidence for any major difference between participants treated with ISBCS and those treated with DSBCS. However, there was a significant heterogeneity between individual studies regarding postoperative complications, most likely due to different definitions between studies, and most studies excluded people at risk of complications. Finally, regarding cost-effectiveness, only one study reported cost-effectiveness ratios (Malvankar-Mehta 2013). However, since unfair assumptions were made with regard to QALYs and costs were calculated erroneously in this study, we have little confidence in the corresponding results on cost-effectiveness of ISBCS compared to DSBCS. Five partial economic evaluations reported on total patient costs. Although results on total costs could not be pooled due to differences in cost sources and time horizon employed, all included studies reported lower costs for ISBCS compared to DSBCS.

With respect to secondary outcomes (PROMs, BCDVA), we found no evidence of a difference between treatments for either outcome. However, for BCDVA at one to three months after surgery, results could not be pooled due to heterogeneity and no change from baseline values were available. Studies used a variety of PROMs (i.e. Visual Function Index, CS-5 score, trouble with vision, and patient satisfaction with vision), but results could only be pooled for change in visual function between baseline and one to three months after surgery.

Overall completeness and applicability of evidence

All studies included in this review addressed the interventions under investigation (ISBCS and DSBCS) in relevant participants. However, it should be noted that the studies of Buchan 2020, Herrinton 2017, Kim 2015, and O'Brien 2010 did not include information on the extent of adherence to the general principles (published in 2009) (Arshinoff 2012) for performing ISBCS or the use of antibiotic or anti-inflammatory drug (or both) protocols. In addition, data were not available for all intended outcomes. From the included studies, no data could be included regarding the outcome of cost-effectiveness (expressed as total costs per QALY). Therefore, this review highlights the need for cost-effectiveness studies comparing ISBCS and DSBCS that are performed according to preferred methods for calculation of QALYs (Drummond 2015).

Regarding other outcomes, there was limited evidence from RCTs. Only two RCTs were included in the review, and results of these studies showed high heterogeneity regarding complications and BCDVA. In addition, although the PROMs evaluated in this review were mainly based on a validated questionnaire on visual function, different types and different generations of PROMs are available. Evidence in this review represents results from the Visual Function Questionnaire that is not corrected for external validity using Rasch analysis (such as the Catquest-9SF questionnaire). In addition, even though PROMs at one week after surgery were included as an outcome of interest in the protocol for this review, none of the included studies provided data on this outcome (Dickman 2019). Future studies should investigate the potential patient-reported benefit of ISBCS over DSBCS during the interval between first and second eye surgery. Furthermore, only one RCT reported refractive outcomes. The certainty of the evidence provided by this RCT was moderate, but still this study was powered to investigate differences within 2 dioptres of target refraction, while internationally accepted outcomes are usually focussed on deviations within 1.0 or 0.5 dioptres of target (Lundström 2018). Furthermore, there was no information regarding protocol for adjustment of IOL power in second eyes based on refractive outcomes of first eyes in DSBCS. However, since none of the studies reported measuring refractive outcomes one week after surgery, it is unlikely that they would have corrected for any refractive surprise prior to second eye surgery in DSBCS-treated participants. Data on refractive outcomes were available from only one RCT, and additional evidence included from three NRSs did not increase the certainty of the evidence. In addition, the risk of bias in these NRSs was higher (e.g. due to risk of confounding). Therefore, it would be useful to have additional published studies that investigate refractive outcomes, to support the current findings and increase the certainty of the results.

With respect to endophthalmitis, data derived from both RCTs comprised numbers of participants that were too small to adequately estimate the effect of the intervention group on endophthalmitis rates due to the rarity of this event. However, the evidence added by NRSs considerably increased the number of eyes evaluated, improving the estimate on the incidence of this rare yet sight-threatening complication occurring unilaterally. Our findings suggest there is little or no difference in the incidence of unilateral endophthalmitis between ISBCS and DSBCS. Nonetheless, it should be noted that incidences of endophthalmitis

and other complications may vary between countries. Reported incidences range from 0% to 0.08% for intracameral cefuroxime use and 0% to 0.053% for moxifloxacin use, with most of the data originating from Europe, Canada, the USA, and India (Grzybowski 2021a). Furthermore, current evidence provides no information on the methods for diagnosis, the severity, or course of disease in cases of unilateral endophthalmitis. Although the studies found no cases of bilateral endophthalmitis, the estimated risk of the event occurring bilaterally is extremely rare and included numbers of eyes are therefore not large enough to exclude potential harm or benefit. Further considerations regarding the applicability of this evidence in relation to implications for practice are described in the Authors' conclusions.

As for reported costs, there were considerable differences in cost sources and time horizon employed between studies, so that results could not be pooled. In addition, included studies were mainly conducted in single centres, which may limit external validity. Future studies that evaluate costs or cost-effectiveness should provide transparent information with regard to currency, currency year, and volumes of resources used, in order to improve the ability to translate results on costs to different settings (different countries).

Unfortunately, there was no information that allowed comparisons of selected patient groups (e.g. people with medical reasons for undergoing ISBCS, people with ocular comorbidities versus no ocular comorbidities), or comparisons of high-income countries versus LMICs. In addition, it is noteworthy that none of studies included in this review were conducted in low-income countries.

Finally, the comparisons we performed did not consider different baseline characteristics of eyes assigned to ISBCS versus DSBCS, or the correlation between both eyes of the same participant. This is expected to be particularly of influence in NRSs. However, we could not perform sensitivity analyses with exclusion of high, serious, or critical risk of bias studies, since only one study would be left in the comparison (Serrano-Aguilar 2012).

Quality of the evidence

In summary, the overall risk of bias for RCTs ranged from 'some concerns' to 'high risk of bias', depending on the outcome evaluated (i.e. 'high to some concerns' for complications, 'some concerns' for refractive outcomes and BCDVA, and 'high' for PROMs). This was mainly due to potential for bias in reporting, and bias in measurement of the outcome due to inability of blinding in general and unclear influence of postponing second-eye surgery on reported complications. For NRSs, we graded the overall risk of bias as moderate to critical (i.e. 'serious' regarding complications and 'serious to critical' with regard to refractive outcomes). Potential sources of bias mainly included confounding, bias regarding selection of participants and the reported results, and a potential for immortal time bias. Furthermore, for economic evaluations, one study was at critical risk of bias in a way that results could not be included in the review, whereas the other economic studies were graded at potentially serious risk of bias for various reasons as described earlier.

Regarding the certainty of evidence for each comparison, an overview is presented in Summary of findings 1 and Summary of findings 2. Because the severity of risk of bias and certainty of the evidence differed between RCTs and NRSs, we provided separate summary of findings tables for both study types.

The certainty of the evidence for endophthalmitis was graded low for RCTs, due to downgrading two levels for imprecision, because of very small sample sizes compared to the likelihood of occurrence of the event. For NRSs, a higher total number of participants could be included, but the certainty of the evidence was low, downgrading one level because of serious risk of bias and one level for imprecision. The certainty of the evidence on refractive outcomes was moderate for RCTs and low for NRSs. For both RCTs and NRSs, we downgraded one level for imprecision since the CI of the effect failed to exclude important benefit or harm. The evidence from NRSs was downgraded one additional level due to serious risk of bias. For complications, the certainty of the evidence was very low for both RCTs and NRSs, downgrading one level for high/serious risk of bias, one level for inconsistency (as a result of high heterogeneity), and one level for imprecision of the results. With respect to PROMs, we graded the evidence as moderate because of high risk of bias regarding measurement of the outcome in all studies (participants were aware of intervention received). Furthermore, the evidence on BCDVA was very low, downgrading one level for inconsistency, one level for indirectness of the outcome, and one level for imprecision. Finally, regarding costs, the evidence was low for RCTs (due to risk of bias and indirectness) and very low for NRSs (due to risk of bias and differences in included cost sources and time horizons employed).

Since there were fewer than 10 trials in each of the meta-analyses performed, we did not assess publication bias by constructing funnel plots.

Potential biases in the review process

The Cochrane Eye and Vision Group performed a comprehensive literature search. To limit bias in the review process, two review authors independently assessed eligibility of studies and risk of bias in included studies. In addition, two review authors independently performed data-extraction to minimise additional bias. We attempted to obtain additional data from study authors, but we were unable to include any further data. However, despite the thorough search carried out in this review, it is possible that we did not identify other sources of unpublished data. Furthermore, including non-randomised evidence is a potential for additional bias compared to evidence from RCTs only. However, as described in the Types of studies section of this review, inclusion of NRSs is more representative for rare outcomes, and an appropriate tool for assessment of these types of studies (the ROBINS-I tool) was used to take into account potential biases. In addition, we presented the results from RCTs and NRSs both separately and combined.

Agreements and disagreements with other studies or reviews

One systematic review and meta-analysis that included RCTs only reported the evidence regarding complications (including the risk of endophthalmitis) in ISBCS versus DSBCS to be of very low to moderate quality (Kessel 2015). In addition, they reported a high inconsistency in incidences of complications between studies, most likely as a result of differences in definitions of complications. Furthermore, they indicated the included number of participants was too small to identify important rare complications such as endophthalmitis. These findings are in agreement with our analysis

of RCT data. However, next to data from RCTs, we included data from NRSs on the incidence of endophthalmitis. We found no evidence of a difference in unilateral endophthalmitis risk for ISBCS versus DSBCS, with an absolute risk for ISBCS of 0.019% (95% CI 0.003 to 0.12%). Nonetheless, this absolute risk (most importantly, the upper CI) could not exclude harm for unilateral endophthalmitis incidence compared to rates reported in recent literature (Grzybowski 2021a). In addition to the results on complications, Kessel 2015 aimed to report anisometropia as an outcome for refractive results. However, no data on this outcome could be included. They did not evaluate refractive surprise or the deviation from target refraction, as evaluated in our review. Finally, regarding PROMs, they found no difference in subjective visual function at one to two months after surgery, in agreement with our analysis. Kessel 2015 did not evaluate costs or cost-effectiveness outcomes.

Another systematic review and meta-analysis by Malvankar-Mehta and colleagues included journal articles, meta-analyses, systematic reviews, NRSs, and cost-evaluation studies next to RCTs, and reported on utility scores (using TTO, VF-14, VF-7, Catquest, EuroQol-5 Dimension (EQ-5D) and Health Utilities Index – 3 (HUI-3) questionnaires), best-corrected visual acuity, and complications (Malvankar-Mehta 2015). However, this review erroneously included articles that did not compare ISBCS and DSBCS, but first-eye and second-eye surgery in DSBCS-treated participants in the meta-analysis for results of ISBCS versus DSBCS (Busbee 2002; Busbee 2003; Castells 2006; Gothwal 2011; Hiratsuka 2011). Therefore, the analyses performed regarding postoperative BCDVA and included PROMs/utilities (i.e. results on TTO, EQ-5D, HUI-3, and visual function) could not be compared to the results of our review. Furthermore, they reported a significant improvement in Catquest questionnaires in favour of ISBCS. However, these results were derived from study types other than RCTs, leading to an increased risk of bias. Reporting of result on complications was limited to a narrative description of percentages reported in both groups in included studies with no overall conclusions, and could therefore not be compared to results from our meta-analysis. The quality of the evidence in the review of Malvankar-Mehta 2015 was assessed using a Downs and Black checklist, and graded at high, medium, and poor quality, but no further details regarding the assessments or results per included study were provided. Although cost-analysis studies were among the studies included in the review, there was no information was provided on cost-outcomes or cost-effectiveness for ISBCS versus DSBCS.

In one narrative literature review by Lansingh and colleagues (albeit not performed using a systematic approach for identification of studies) reported no evidence for major differences in complication rates, including risk of endophthalmitis, between ISBCS and DSBCS (Lansingh 2015). In addition, they described lower costs for ISBCS compared to DSBCS in several cost-analysis studies. This is in line with the findings in this review.

While this review was close to be published, Malwankar 2021 was published and provided more data on demographics of people receiving ISBCS, and rates of postoperative endophthalmitis and cystoid macular oedema for ISBCS versus DSBCS. Similar to our review, they reported no evidence for major differences regarding postoperative endophthalmitis and other complications (i.e. cystoid macular oedema) between groups.

To our knowledge, no other systematic reviews evaluating the costs and cost-effectiveness of ISBCS versus DSBCS are available to date.

AUTHORS' CONCLUSIONS

Implications for practice

Cataract surgery is a high-volume procedure. Ageing of the population and increasing global healthcare expenditure warrant a fresh view on how to address these challenges in the most cost-effective way.

Immediate sequential bilateral cataract surgery (ISBCS) offers a potential solution and has become highly topical during the recent COVID-19 pandemic, dictating a reduction in patient contacts, and limiting access to elective surgery.

Implications for practice should first consider patient's safety. Although current evidence from this review supports there is likely no significant difference in clinical outcomes between ISBCS and delayed sequential bilateral cataract surgery (DSBCS) such as endophthalmitis, refractive outcomes, and other complications, the amount and certainty of evidence is limited. Regarding unilateral endophthalmitis, relatively low numbers of ISBCS-treated participants were included in the literature compared to DSBCS. Moreover, how endophthalmitis was diagnosed and the severity of reported events remains unclear, and none of the studies were sufficiently powered to detect bilateral endophthalmitis. Although the risk of bilateral endophthalmitis is extremely low, it has a potentially devastating impact. An overview of case reports by Arshinoff 2009 showed that two of four reported bilateral endophthalmitis cases resulted in bilateral blindness, whereas the other cases recovered to a visual acuity of 20/40 and 6/9. Changes in practice patterns regarding for instance (standard) use of intracameral antibiotics could limit the impact of endophthalmitis over time. Moreover, the estimated risk of bilateral endophthalmitis reported by Arshinoff 2012 is one in 70 million, taking into account a correlation between both eyes of one patient. However, it should be noted this risk was estimated based on a unilateral endophthalmitis risk of one in 14,352, while endophthalmitis rates vary between countries. A report on acceptability or tolerability of risks (i.e. regarding the probability of injury, disease, or death under specific circumstances) by the World Health Organization (WHO) (WHO 2001) could provide a framework on how to evaluate acceptable risk incidences for postoperative complications. In this report, they described the use of a predefined probability of 'essentially zero', and indicated that a risk of one in 1,000,000 was adapted by the Food and Drug Administration as a gold standard. This probability was also accepted by the UK Health and Safety Executive (HSE). Nonetheless, the WHO indicates that tolerability of risks should also be based on other factors such as the public acceptance of the risk.

With respect to refractive outcomes, one advantage of DSBCS includes the possibility to adjust second-eye surgery plans based on first-eye refractive outcomes (Olsen 2011). The studies included in the current review provided low- to moderate-certainty evidence that there is no difference in the percentage of eyes that failed to achieve refraction within 1.0 dioptre of target. However, it is unknown whether protocols for intraocular lens (IOL) adjustment in the second eye were used, and whether a benefit was conveyed to patients. Meanwhile, the question remains whether this is often applied in current clinical practice, since even randomised

controlled trials (RCTs) and non-randomised studies (NRSs) about ISBCS do not report protocols for adjustment of IOL selection for the second eye based on first eye outcomes in DSBCS-treated participants (Cholevik 2015; Chung 2009; Herrinton 2017; Nassiri 2009; Sarikkola 2011). Hence, besides refractive outcome, future studies should include details on IOL adjustment in the second eye and whether it conveys benefit to patients.

Regarding complications and outcomes in general, it should be noted that most studies excluded patients at risk. In practice, this means that the results of this review should be interpreted in the context of critical patient selection criteria and should not be extrapolated to all types of patients. Future studies are needed to refine ISBCS selection criteria.

This review showed lower costs for ISBCS compared to DSBCS. However, there is a need for well-designed cost-effectiveness studies. High-quality evidence on cost-effectiveness can contribute to financial discussions between healthcare providers and payers.

Finally, performing the ISBCS procedure may result in financial pressure in current practice. This is because ophthalmologists may receive lower reimbursement for cataract surgery of the second eye, discouraging them from performing ISBCS (Ahmed 2021; Arshinoff 2006; Masket 2021). However, financial motives may push lower income countries towards performing ISBCS while safety and effectiveness risks may be higher.

Implications for research

This review highlights the need for cost-effectiveness studies that compare ISBCS and DSBCS. In addition, future studies that investigate refractive outcomes and large NRSs or (randomised) registry studies that measure endophthalmitis rates could increase the certainty of the current findings. Furthermore, a standardised way of reporting best-corrected distance visual acuity is required to pool results for this outcome, and there is a need to reduce variability in definitions and reporting of complications. Also, future studies should evaluate PROMs and (vision-related) quality of life in the early postoperative period for ISBCS versus DSBCS. Finally, future studies are required to further investigate ISBCS in selected patient populations and low-income countries.

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Zuo 2015

Zuo L, Zou H, Fei X, Xu W, Zhang J.The impact of unilateral or bilateral cataract surgery on visual acuity and life quality of elderly patients. *Journal of Ophthalmology* 2015;**2015**:Article ID 509049. [DOI: 10.1155/2015/509049]

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Dickman 2019

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Buchan 2020

Study characteristics	
Methods	*Study design:* retrospective cohort study
Participants	*Country:* UK *Total number:* 249,414 *Mean age:* ISBCS 71.5 (range 21.4–100.6); DSBCS 75.6 (range 18.0–112.5) years *Sex (male):* ISBCS: 37.5%; DSBCS: 39.9% *Inclusion criteria:* aged ≥ 18 years, undergoing cataract surgery using phacoemulsification, where the primary intention was not a combined surgery with another procedure. Contributing centres had to have performed ≥ 50 eligible cataract operation between 1 April 2010 and 31 August 2018 and ≥ 1 record of an ISBCS operation *Exclusion criteria:* NR

Buchan 2020 *(Continued)*

	Eyes reported: both
Interventions	*Intervention:* ISBCS *Intervention number of people:* 1073 *Intervention number of eyes:* 2146 *Comparator:* DSBCS (second-eye surgery within 1 year of first-eye surgery) *Comparator number of people:* 248,341 *Comparator number of eyes:* 496,682
Outcomes	*Primary outcomes:* intraoperative complications, posterior capsule rupture, endophthalmitis, preoperative visual acuity *Secondary outcome:* NR *Adverse events reported:* yes, operative complications and endophthalmitis rates *Follow-up length:* unclear *Follow-up times:* unclear
Notes	*Trial registration:* no *Trial registration number:* NA *Date conducted (recruitment):* 1 April 2010 to 31 August 2018 *Source(s) of funding:* The Healthcare Quality Improvement Partnership (HQIP) commissioned Royal College of Ophthalmologists (RCOphth) National Ophthalmology Database Audot, which is part of the National Clinical Audit and Patient Outcomes Programme (NCAPOP) and the Clinical Outcomes Programme (COP). Salary: Queen Elizabeth Diamond Jubilee Trust, Commonwealth Eye Health Consortium. *Declaration/conflicts of interest:* none

Cholevik 2015

Study characteristics	
Methods	*Study design:* retrospective cohort study
Participants	*Country:* Czech Republic *Total number:* 100 *Mean age:* ISBCS: 72.22 (SD 6.8; range 53–89); DSBCS: 74.04 (SD 6.23; range 58–88) years *Sex (% male):* ISBCS: 36%; DSBCS: 42% *Inclusion criteria:* bilateral cataract with indication for bilateral surgery by the same surgeon and the same monofocal IOL type *Exclusion criteria:* immunosuppressive/immunomodulatory therapy, endothelial dystrophy (< 1300 cells/mm^2), chronic/recurring uveitis, Possner-Schlossman syndrome, severe pseudoexfoliation syndrome, severe age-related macular degeneration, active inflammation of the eye or adnexa, multifocal lenses, toric lenses, monofocal lenses other than AcrySof SA60AT

Cholevik 2015 *(Continued)*

	Eyes reported: both
Interventions	*Intervention:* ISBCS *Intervention number of people:* 50 *Intervention number of eyes:* 100 *Comparator:* DSBCS *Comparator number of people:* 50 *Comparator number of eyes:* 100
Outcomes	*Primary outcome:* unclear *Secondary outcomes:* intraoperative complications, subjective refraction, uncorrected and best-corrected visual acuity, postoperative complications, intraocular pressure *Adverse events reported:* yes *Follow-up length:* 3 months *Follow-up times:* 1 day (ISBCS only), 1 week, 1 month, 3 months
Notes	*Trial registration:* no *Trial registration number:* NA *Date conducted (recruitment):* 26 March 2012 to 4 July 2012 *Source of funding:* NR *Declaration/conflicts of interest:* NR

Chung 2009

Study characteristics	
Methods	*Study design*: non-randomised controlled trial
Participants	*Country:* South Korea *Total number:* 194 *Mean age:* ISBCS: 66.38 (SD 9.41); DSBCS: 65.32 (SD 11.11) years *Sex (% male):* ISBCS: 41.5%; DSBCS: 42% *Inclusion criteria:* bilateral phacoemulsification with posterior chamber IOL implantation *Exclusion criteria:* corneal opacity, corneal endothelial dystrophy, uveitis, previous refractive correction surgery, unreliable biometric measurements due to abnormalities of the cornea and retina, ophthalmological or neurological diseases affecting visual acuity, previous ophthalmological operations, short follow-up period, insufficient examination data, incomplete questionnaires or refusal to complete questionnaires *Eyes reported:* both
Interventions	*Intervention:* ISBCS *Intervention number of participants:* 94

Chung 2009 *(Continued)*

	Intervention number of eyes: 188
	Comparator: DSBCS (with second-eye surgery on 2 days after first-eye surgery)
	Comparator number of participants: 100
	Comparator number of eyes: 200
Outcomes	*Primary outcome:* unclear
	Secondary outcomes: changes in refraction and visual acuity, degree of anisometropia, occurrence rates of intraoperative and postoperative complications, degree of satisfaction with simultaneous bilateral cataract surgery
	Adverse events reported: yes
	Follow-up length: 3 months
	Follow-up times: 1 day, 1 week, 1 month, 3 months
Notes	*Trial registration:* no
	Trial registration number: NA
	Date conducted (recruitment): NR (period of 18 months)
	Source of funding: NR
	Declaration/conflicts of interest: NR

Herrinton 2017

Study characteristics	
Methods	*Study design:* retrospective cohort study
Participants	*Country:* USA
	Total number: 24,615
	Mean age (range): NR
	Sex (% male): ISBCS: 39%; DSBCS: 38%
	Inclusion criteria: undergoing cataract surgery of both eyes within 1 year or on the same day
	Exclusion criteria: complex phacoemulsification cases and cases performed by glaucoma, oculoplastic or retinal specialists, as well as procedures by any surgeon combined with corneal transplant or glaucoma surgery. Previous endophthalmitis, absence of manifest refraction for postoperative BCVA analysis, second surgery performed > 1 year after first eye, 1 year enrolment prior to first-eye surgery
	Eyes reported: both
Interventions	*Intervention:* ISBCS
	Intervention number of participants: 5247
	Intervention number of eyes: 10,494
	Comparator: DSBCS (second-eye surgery within 1 year of first-eye surgery)
	Comparator number of participants: 19,368

Herrinton 2017 *(Continued)*

	Comparator number of eyes: 38,736
Outcomes	*Primary outcome:* unclear *Secondary outcomes:* visual acuity, refraction, surgical complications *Adverse events reported:* yes *Follow-up length:* 1 year *Follow-up times:* refractive error: nearest date to surgery from 3 weeks to 1 year after surgery. Complication: during surgery and up to 120 days after surgery
Notes	*Trial registration:* no *Trial registration number:* NA *Date conducted (recruitment):* 1 January 2013 to 30 June 2015 *Sources of funding:* Garfield Memorial Fund, Kaiser Permanente, and the National Eye Institute (NEI R01 EY027329) *Declaration/conflicts of interest:* Kaiser Permanente potentially derives a benefit from improvements in operating room and clinic efficiency an implementation of immediate sequential bilateral cataract surgery, and this represents a potential conflict of interest.

Kim 2015

Study characteristics	
Methods	*Study design:* retrospective cohort study
Participants	*Country:* Korea *Total number:* 140 participants (280 eyes) *Mean age:* ISBCS: 71.2 (SD 6.9); DSBCS: 70.3 (SD 8.6) years *Sex (% male):* NR *Inclusion criteria:* had cataract surgery performed from January 2010 to December 2014 *Exclusion criteria:* history of ophthalmic diseases or trauma that can affect postoperative vision, complications during surgery *Eyes reported:* both
Interventions	*Intervention:* ISBCS *Intervention number of participants:* 70 *Intervention number of eyes:* 140 *Comparator:* DSBCS (second eye 1–2 months after first-eye surgery) *Comparator number of participants:* 70 *Comparator number of eyes:* 140
Outcomes	*Primary outcome:* unclear

Kim 2015 *(Continued)*

	Secondary outcomes: BCVA, manifest spherical equivalent and refractive error, incidence of endophthalmitis *Adverse events reported:* no *Follow-up length:* 1 month *Follow-up time:* 1 month
Notes	*Trial registration:* no *Trial registration number:* NA *Date conducted (recruitment):* January 2010 to December 2014 *Source of funding:* NR *Declaration/conflicts of interest:* NR

Leivo 2011

Study characteristics	
Methods	*Study design:* randomised controlled trial-based cost analysis *Year of study:* 2011 *Sources of resource use:* patient charts, hospital internal accountancy, floor-space measurements and work-time questionnaires to physicians and nurses. Potential for optimum floor time, staff time, mean operating times and change times were estimated using an internal audit of 7000 cataract surgeries performed from 2004 to 2006. Public economic and statistical databases were used to complete health-cost accounting. Non-healthcare costs: detailed interview questionnaires and a telephone interview 3 months after surgery (among random subgroup of participants) *Decision-making jurisdiction:* Finland *Geographical setting:* Finland *Organisational setting:* Helsinki University Eye Hospital *Currency:* EUR *Currency year:* 2006 *Perspective costs:* societal *Perspective effects:* NR *Time horizon costs:* 3 months *Time horizon effects:* NR
Participants	*Country:* Finland *Total number:* 520 (241 participants included in non-healthcare and time-cost analysis) *Mean age:* unclear for the cost-analysis subgroup *Sex (% male):* unclear for the cost-analysis subgroup *Inclusion criteria (derived from Sarikkola 2011):* aged ≥ 18 years, visually significant bilateral cataract, CDVA in the better eye ≤ 20/40, CDVA > 20/40 but VF-7 < 70 or predicted postoperative anisometropia

Leivo 2011 *(Continued)*

	≥ 2.0 dioptres and CDVA in the second eye ≤ 20/25, axial length 21.5–26.0 mm and difference between eyes ≤ 1.5 mm, phacoemulsification under topical anaesthesia with sedation/intracameral anaesthesia (or both) applied as necessary taking into consideration the general condition, hearing and co-operation of the patient, patient had an escort available in case of randomisation to same-day surgery, gave written informed consent and is available for follow-up *Exclusion criteria (derived from Sarikkola 2011):* conditions that increase the risk of infection (blepharitis, conjunctivitis, dacrocystitis); immunosuppressive disease (leukaemia, lymphoma); immunosuppressive medication (corticosteroids); conditions that increase the risk for corneal oedema (Fuchs dystrophy or cornea guttata); abnormal eye, adnexal, or anatomical abnormality that would interfere with surgery; previous refractive surgery; previous perforating or severe blunt eye injury, lens luxation or iridodonesis; glaucoma or intraocular pressure > 24 mmHg; uncontrolled systemic hypertension; iodine allergy *Eyes reported:* both
Interventions	*Intervention:* ISBCS *Intervention number of participants: unclear* *Comparator:* DSBCS *Comparator number of participants: unclear*
Outcomes	*Primary outcome:* cost per participant for ISBCS compared to DSBCS *Secondary outcome:* NA *Adverse events reported:* no (reported in Sarikkola 2011) *Follow-up length:* 3 months *Follow-up time:* preoperatively, 1 day and 1 month after each surgery. Telephone interview at 3 months
Notes	*Trial registration:* no *Trial registration number:* NA *Date conducted (recruitment): May* 2002 to February 2005 *Sources of funding:* research grants from the Eye and Tissue Bank Foundation, Eye Foundation, Evald and Hilda Nissi Foundation, Finnish Medical Foundation, and the Helsinki University Central Hospital Research Fund (TYH3234, TYH4227) *Declaration/conflicts of interest:* no financial or proprietary interest *Sensitivity analysis performed:* no Risk of bias reported in Table 1; Table 2

Lundstrom 2009

Study characteristics	
Methods	*Study design:* model-based cost analysis *Year of study:* 2009 *Sources of resource use:* previously published investigation on costs (Lundstrom 2000) *Decision-making jurisdiction:* Sweden

Lundstrom 2009 *(Continued)*

	Geographical setting: Sweden
	Organisational setting: single hospital (Department of Ophthalmology, Karlskrona, Sweden)
	Currency: SEK
	Currency year: unclear
	Perspective costs: health care
	Perspective effects: NR
	Time horizon costs: unclear, until final postoperative visit. Mean time between DSBCS surgeries: 5.5 (SD 4.6) months
	Time horizon effects: unclear
Participants	*Country:* Sweden
	Total number: 97
	Mean age: 77.9 (SD 9) years
	Sex (% male): 28%
	Inclusion criteria: undergoing ISBCS or DSBCS from December 2005 to April 2006
	Exclusion criteria: people with an unusually long waiting time for personal reasons
	Eyes reported: both
Interventions	*Intervention:* ISBCS
	Intervention number of people: 17
	Intervention: DSBCS
	Intervention number of people: 80
Outcomes	*Primary outcomes:* resource utilisation, costs, capability index
	Secondary outcome: NA
	Adverse events reported: no
	Follow-up length: unclear
	Follow-up time: unclear
Notes	*Trial registration:* no
	Trial registration number: NA
	Date conducted (recruitment): December 2005 to April 2006
	Source of funding: grants from the County of Blekinge, Karlskrona, Sweden
	Declaration/conflicts of interest: NR
	Sensitivity analysis performed: no
	Risk of bias reported in Table 1; Table 3

Malvankar-Mehta 2013

Study characteristics	
Methods	*Study design:* model-based cost-analysis (decision tree model) *Year of study:* 2013 *Sources of resource use:* a systematic review was performed for determining outcomes and complications to be used in the model. (Criteria for inclusion: publication in English language, phacoemulsification on humans aged > 19 years, publication dates from 2000 and onwards). Utilities were based on a single study. Probabilities, medical costs, and utility values used in the model were also obtained from a comprehensive systematic review.) *Decision-making jurisdiction:* Canada *Geographical setting:* Canada *Organisational setting:* unclear *Currency:* CAD *Currency year:* unclear *Perspective costs:* payer *Perspective effects:* payer *Time horizon costs:* unclear *Time horizon effects:* unclear
Participants	*Country:* Canada *Total number:* NA *Mean age:* NA *Sex (% male):* NA *Inclusion criteria:* NA *Exclusion criteria:* NA *Eyes reported:* NA
Interventions	*Intervention:* ISBCS *Intervention number of people:* NA *Intervention number of eyes:* NA *Comparator:* DSBCS *Comparator number of people:* NA *Comparator number of eyes:* NA
Outcomes	*Primary outcome:* cost-effectiveness *Secondary outcome:* unclear *Adverse events reported:* NA *Follow-up length:* NA *Follow-up time:* NA

Malvankar-Mehta 2013 *(Continued)*

Notes	*Trial registration:* NA *Trial registration number:* NA *Date conducted (recruitment):* NA *Source of funding:* annual grant "Baker New Researcher Fund" from the Canadian National Institute of the Blind *Declaration/conflicts of interest:* none reported *Sensitivity analysis performed:* yes *Impact of varying assumptions on magnitude and direction of the results:* no influence of changes in complication rates or costs of intravitreal injections or topical medications no influence of changes in complication rates or costs of intravitreal injections or topical medications

Nassiri 2009

Study characteristics	
Methods	*Study design*: non-randomised controlled trial
Participants	*Country:* Iran *Total number:* 220 *Mean age:* ISBCS: 67.31 (SD 7.2); DSBCS: 66.56 (SD 5.6) years *Sex (% male):* ISBCS: 45%; DSBCS: 46.4% *Inclusion criteria:* all consecutive patients with bilateral, visually significant cataract *Exclusion criteria:* increased risk of endophthalmitis (e.g. active adnexal and ocular surface infection, immunosuppression and immunodeficiency, systemic steroids, diabetes mellitus), axial extremes (axial length > 27 mm or < 21 mm), posterior segment disorders, pre-existing ocular comorbidities (e.g. pterygium, glaucoma, phacodonesus, and corneal opacity), history of previous ocular surgeries (e.g. trabeculectomy, refractive surgery), history of ocular trauma, and intraoperative complications during the first-eye surgery (e.g. vitreous loss, posterior capsule rupture, very prolonged surgery due to surgical difficulties) *Eyes reported:* both
Interventions	*Intervention:* ISBCS *Intervention number of people:* 80 *Intervention number of eyes:* 160 *Comparator:* DSBCS (2 months between first- and second-eye surgery) *Comparator number of people:* 140 *Comparator number of eyes:* 280
Outcomes	*Primary outcomes:* binocular visual acuity, binocular contrast sensitivity, and stereopsis, participant-reported visual disability score (VF-14) *Secondary outcome:* NR *Adverse events reported:* yes

Nassiri 2009 *(Continued)*

	Follow-up length: 4 months (ISBCS) and 6 months (DSBCS)
	Follow-up times: 2 months and 4 months after second-eye surgery
Notes	*Trial registration:* no
	Trial registration number: NA
	Date conducted (recruitment): January 2004 to September 2005
	Source of funding: NA
	Declaration/conflicts of interest: no conflicts of interest

Neel 2014a

Study characteristics	
Methods	*Study design:* model-based cost analysis
	Year of study: 2014
	Sources of resource use: Medicare reimbursement schedules for West Tennessee and national means, data provided by the Physicians Surgery Center, Jackson, Tennessee and from the Eye Clinic, PC, Jackson Tennessee. Patient driving distances were calculated from the office address to the patient's residence using MapQuest and the Internal Revenue Service 2012 standard mileage reimbursement rate for medical purposes. Lost time from work was calculated using the 2011 West TN mean hourly wage rate and the 2011 national mean hourly wage rate
	Decision-making jurisdiction: USA
	Geographical setting: USA
	Organisational setting: ambulatory surgery centre and a hospital outpatient department
	Currency: USD
	Currency year: 2012
	Perspective costs: payer, participant, societal
	Perspective effects: NA
	Time horizon costs: unclear
	Time horizon effects: NA
Participants	*Country:* USA
	Total number: NA
	Mean age: NA
	Sex (% male): NA
	Inclusion criteria: NA
	Exclusion criteria: NA
	Eyes reported: NA
Interventions	*Intervention:* ISBCS

Neel 2014a *(Continued)*

	Intervention number of people: NA
	Intervention: DSBCS
	Intervention number of people: NA
Outcomes	*Primary outcome:* costs
	Secondary outcome: NA
	Adverse events reported: no
	Follow-up length: unclear
	Follow-up time: unclear
Notes	*Trial registration:* no
	Trial registration number: NA
	Date conducted (recruitment): 2012
	Source(s) of funding: none reported
	Declaration/conflicts of interest: none reported
	Sensitivity analysis performed: no
	Risk of bias reported in Table 1; Table 3

O'Brien 2010

Study characteristics	
Methods	*Study design:* non-randomised trial-based cost analysis
	Year of study: 2010
	Sources of resource use: hospital/patient registration system (the LHSC case-costing system)
	Decision-making jurisdiction: Canada
	Geographical setting: Canada
	Organisational setting: single hospital (London Health Sciences Centre)
	Currency: CAD
	Currency year: unclear
	Perspective costs: health care
	Perspective effects: NA
	Time horizon costs: unclear, surgical costs only (short-term)
	Time horizon effects: NA
Participants	*Country:* Canada
	Total number: 44
	Mean age: NR

O'Brien 2010 *(Continued)*

	Sex (% male): NR
	Inclusion criteria: undergoing ISBCS or DSBCS with routine phacoemulsification with implantation of a posterior chamber IOL, with no intraoperative complications or procedures that would influence costing analysis
	Exclusion criteria: underwent additional surgical procedures at the same time as the cataract surgery
	Eyes reported: NA
Interventions	*Intervention:* ISBCS
	Intervention number of people: 22
	Intervention: DSBCS
	Intervention number of people: 22
Outcomes	*Primary outcome(s):* hospital-based surgical costs
	Secondary outcome(s): NA
	Adverse events reported: no
	Follow-up length: surgery only
	Follow-up time: surgery only
Notes	*Trial registration:* no
	Trial registration number: NA
	Date conducted (recruitment): May 2002 to April 2003
	Source of funding: NR
	Declaration/conflicts of interest: no conflicts of interest
	Sensitivity analysis performed: no
	Risk of bias reported in Table 1; Table 2

Rush 2015

Study characteristics	
Methods	*Study design:* prospective non-randomised trial-based cost analysis
	Year of study: 2015
	Sources of resource use: expenses and costs: billing reports, invoices, receipts. ASC facility and surgery times: notes in the charts that were recorded by ASC circulating nurses. Distances and times spent: calculated by inputting directions from the patient's residing address and the physical address of the ASC into Google Maps
	Decision-making jurisdiction: USA
	Geographical setting: USA
	Organisational setting: single private-practice ambulatory surgery centre
	Currency: USD

Rush 2015 *(Continued)*

	Currency year: unclear
	Perspective costs: payer
	Perspective effects: NR
	Time horizon costs: 90 (SD 14) days
	Time horizon effects: NR
Participants	*Country:* USA
	Total number: 84
	Mean age: ISBCS: 66.3 (95% CI 63.1 to 69.5); DSBCS: 65.9 (95% CI 62.7 to 69.1) years
	Sex (% male): ISBCS: 57.1%; DSBCS: 50%
	Inclusion criteria: visually significant bilateral cataract; bilateral phacoemulsification with IOL implantation; aged 30–100 years
	Exclusion criteria: unsuitable for topical anaesthesia; known allergy to pharmaceuticals used in the study; visually significant retinal disease; active uveitis; advanced or poorly controlled glaucoma; visually significant corneal disease; history of corneal transplantation or refractive surgery; pseudoexfoliation syndrome; pupillary miosis preoperatively judged to require intraoperative pupillary expansion techniques; immunocompromised
	Eyes reported: both
Interventions	*Intervention:* ISBCS
	Intervention number of people: 42
	Intervention number of eyes: 84
	Comparator: DSBCS (1–3 weeks between first- and second-eye surgery)
	Comparator number of people: 42
	Comparator number of eyes: 84
Outcomes	*Primary outcomes:* comparison of the direct cost for the participant, physician, ASC, and third-party payer
	*Secondary outcomes: i*ntraoperative complications, final CDVA, error in actual refractive outcome from the intended target, postoperative complications
	Adverse events reported: yes
	Follow-up length: 90 days
	Follow-up time: 24 hours from the time of surgery, 21 (SD 5) days after surgery, 90 (SD 14) days after surgery
Notes	*Trial registration:* yes
	Trial registration number: NCT01841957
	Date conducted (recruitment): 2 August 2013 to 27 January 2014
	Source of funding: NR
	Declaration/conflicts of interest: no conflicts of interest
	Sensitivity analysis performed: no

Rush 2015 *(Continued)*

	Risk of bias on cost-analysis reported in Table 1; Table 2; Table 4

Sarikkola 2011

Study characteristics	
Methods	*Study design*: randomised controlled trial
Participants	*Country:* Finland *Total number:* 520 (502 participants underwent surgery out of 507 that were actually enrolled) *Mean age:* ISBCS: 75.3 (SD 7.9) (range: 43–94); DSBCS: 75.0 (SD 8.1) (range: 51–96) years *Sex (% male):* ISBCS: 26.4%; DSBCS: 25.7% *Inclusion criteria:* aged ≥ 18 years, visually significant bilateral cataract, CDVA in the better eye ≤ 20/40, CDVA > 20/40 but VF-7 < 70 or predicted postoperative anisometropia ≥ 2.0 dioptres and CDVA in the second eye ≤ 20/25, axial length 21.5–26.0 mm and difference between eyes ≤ 1.5 mm, phacoemulsification under topical anaesthesia with sedation/intracameral anaesthesia (or both) applied as necessary taking into consideration the general condition hearing and co-operation of the participant, participant has an escort available in case of randomisation to same-day surgery, gave written informed consent and is available for follow-up *Exclusion criteria:* conditions that increase the risk of infection (blepharitis, conjunctivitis, dacrocystitis), immunosuppressive disease (leukaemia, lymphoma), immunosuppressive medication (corticosteroids), conditions that increase the risk for corneal oedema (Fuchs dystrophy or cornea guttata), abnormal eye/adnexal/anatomical abnormality that would interfere with surgery, previous refractive surgery, previous perforating or severe blunt eye injury, lens luxation or iridodonesis, glaucoma or intraocular pressure > 24 mmHg, uncontrolled systemic hypertension, iodine allergy *Eyes reported:* both
Interventions	*Intervention:* ISBCS *Intervention number of people:* 247 *Intervention number of eyes:* 493 *Comparator:* DSBCS (4–6 weeks between first- and second-eye surgery) *Comparator number of people:* 255 *Comparator number of eyes:* 506
Outcomes	*Primary outcome:* proportion of participants with a difference of > 2.0 dioptres between target and achieved refraction in the second eye *Secondary outcomes:* intraoperative and postoperative complications; patient satisfaction with surgery; CDVA; participant-reported visual outcome measures *Adverse events reported:* yes *Follow-up length:* 1 month *Follow-up time:* 1 day and 1 month after each surgery
Notes	*Trial registration:* no *Trial registration number:* NA

Sarikkola 2011 *(Continued)*

	Date conducted (recruitment): 1 May 2002 to 28 February 2005
	Sources of funding: research grants from the Eye and Tissue Bank Foundation, Eye Foundation, Evald and Hilda Nissi Foundation, Finnish Medical Foundation, and the Helsinki University Central Hospital Research Fund (TYH3234, TYH4227)
	Declaration/conflicts of interest: no financial or proprietary interest

Serrano-Aguilar 2012

Study characteristics	
Methods	*Study design*: randomised controlled trial
Participants	*Country:* Spain, Canary Islands
	Total number: 845 participants (1690 eyes)
	Mean age: ISBCS: 72.9 (SD 8.2; range 41–93); DSBCS: 71.7 (SD 7.9; range 33–93) years
	Sex (% male): ISBCS: 38.8%; DSBCS: 39.5%
	Inclusion criteria: bilateral cataracts with a UDVA of 20/40 or worse in each eye due to cataract
	Exclusion criteria: risk factors for endophthalmitis (chronic infections of the eyes or adnexa, immunosuppressive treatment), cataract nigrans or Fuchs dystrophy, previous refractive surgery or myopia with posterior staphylomas, severe concomitant eye conditions that could limit the degree of improvement achievable with surgery, complex cataracts of traumatic origin, Marfan Syndrome, uncontrolled ocular hypertension, diabetes with retinopathy and macular oedema, and cognitive or behavioural impairments that could make surgery with topical anaesthesia problematic or limit the patients' ability to complete the self-evaluation questionnaire.
	Eyes reported: both
Interventions	*Intervention:* ISBCS
	Intervention number of people: 417
	Intervention number of eyes: 834
	Comparator: DSBCS (6 weeks between first- and second-eye surgery)
	Comparator number of people: 390
	Comparator number of eyes: 780
Outcomes	*Primary outcome:* incidence of intraoperative and postoperative complications
	Secondary outcomes: UDVA, CDVA, VF-14
	Adverse events reported: yes
	Follow-up length: 1 year
	Follow-up time: 1 day, 5 days, 1 month, 1 year
Notes	*Trial registration:* no
	Trial registration number: NA
	Date conducted (recruitment): 2008

Serrano-Aguilar 2012 *(Continued)*

Sources of funding: supported by the Spanish Ministry of Health and Consumer Affairs in co-operation with the Canary Islands Foundation for Health and Research within the framework of the Quality Plan for the National Health Service, Madrid, Spain

Declaration/conflicts of interest: no conflicts of interest

ASC: ambulatory surgery centre; BCVA: best-corrected visual acuity; CDVA: corrected distance visual acuity; DSBCS: delayed sequential bilateral cataract surgery; IOL: intraocular lens; ISBCS: immediate sequential bilateral cataract surgery; NA: not available/applicable; NR: not reported; UDVA: uncorrected distance visual acuity; VF-7: Visual Function Index-7.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmed 2021	No original data (e.g. review)
Akcay 2013	No comparative study
Anonymous 2017	No original data (e.g. review)
Arshinoff 2008	No original data (e.g. review)
Arshinoff 2009	No original data (e.g. review)
Arshinoff 2011a	No original data (e.g. review)
Arshinoff 2011b	No original data (e.g. review)
Arshinoff 2012	No original data (e.g. review)
Arshinoff 2019	No original data (e.g. review)
Arshinoff 2020	No original data (e.g. review)
Baartman 2015	Wrong comparator
Behndig 2009	No original data (e.g. review)
Bellan 2011	No original data (e.g. review)
Bueno-Garcia 2014	No comparative study
Callaway 2019	Wrong study design
Chandra 2010	No original data (e.g. review)
Cholevik 2014	No original data (e.g. review)
Clearkin 2010	No original data (e.g. review)
Donaldson 2016	No original data (e.g. review)
Ganesh 2017	No comparative study
Giles 2017	No comparative study

Study	Reason for exclusion
Gothwal 2011	Wrong comparator
Grzybowski 2013	No original data (e.g. review)
Grzybowski 2016	No original data (e.g. review)
Guber 2015	No comparative study
Henderson 2012	No original data (e.g. review)
Hesemann 2020	No comparative study
Hiratsuka 2011	Wrong intervention
Huang 2007	No comparative study
Jhanji 2007	Wrong study design
Johansson 2010	No original data (e.g. review)
Lam 2012	No original data (e.g. review)
Masket 2021	No original data (e.g. review)
Murtagh 2019	No comparative study
Naseri 2014	No original data (e.g. review)
Neel 2014b	Wrong outcomes
Neel 2015a	No original data (e.g. review)
Neel 2015b	No original data (e.g. review)
Olson 2010	No original data (e.g. review)
Rosen 2012	No original data (e.g. review)
Sanmugasunderam 2010	No original data (e.g. review)
Schachat 2014	No original data (e.g. review)
Shorstein 2017	No comparative study
Singh 2017	No original data (e.g. review)
Singh 2020	No original data (e.g. review)
Tatham 2012	No original data (e.g. review)
Wang 2022	Wrong study design

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

NCT01841957

Study name	Immediate simultaneous bilateral cataract surgery: a prospective, case-controlled clinical trial in the United States
Methods	*Study design*: prospective non-randomised clinical trial
Participants	*Country:* USA *Total number (estimated enrolment):* 2000 *Inclusion criteria:* age 30–100 years, candidate for topical anaesthesia, signed the informed consents *Exclusion criteria:* allergies to medications used in the study, cannot have topical anaesthesia, unwilling to participate in research trial, have any other significant ocular comorbidities, known systemic immuno-compromised state
Interventions	*Intervention:* ISBCS (same-day cataract surgery) *Comparator:* DSBCS (bilateral surgery delayed by 1–3 weeks among eyes)
Outcomes	*Primary outcomes:* best uncorrected and best spectacle corrected postoperative visual acuity (time frame: 3 weeks) *Secondary outcomes:* recovery time and number of postoperative visits (time frame: 6 months) *Follow-up length:* 6 months *Follow-up time:* NR
Starting date	April 2013 (estimated study completion date: 1 January 2023)
Contact information	Panhandle Eye Group Amarillo, Texas, USA Contact: Sunday Fowler 806-353-0125 Principal investigator: Sloan Rush
Notes	

NCT03400124

Study name	Cost-effectiveness of immediately versus delayed sequential bilateral cataract surgery (ISBCS vs. DSBCS)
Methods	*Study design:* randomised clinical trial
Participants	*Country:* the Netherlands *Total number (estimated enrolment):* 858 *Inclusion criteria:* bilateral cataract, indication for bilateral cataract surgery, expected uncomplicated surgery *Exclusion criteria:* inability to comply with study procedures or to complete follow-up / Dutch questionnaires, non-routine cataract surgery, cognitive or behavioural conditions that might interfere

NCT03400124 *(Continued)*	
	with surgery, cataract surgery with premium IOL implantation, conditions that increase the risk of endophthalmitis (e.g. current ocular/adnexal/periocular infections, immunocompromised, iodine allergy), factors that increase the risk of refractive surprise (e.g. axial lengths < 21 mm or > 27 mm, difference between eyes of > 1.5 mm, abnormal keratometry readings, previous refractive surgery), conditions that increase the risk of corneal oedema, factors that increase the risk of complicated surgery (e.g. previous surgery, trauma, anatomical abnormalities), sight-threatening comorbidity, glaucoma or IOP > 24 mmHg, uveitis, diabetes with diabetic retinopathy and macular oedema
Interventions	Intervention: ISBCS (cataract surgery in both eyes on the same day) Comparator: DSBCS (cataract surgery in both eyes on separate days, with a time period of ≥ 2 weeks between surgeries)
Outcomes	*Primary outcome*: proportion of participants in both treatment groups with a postoperative refraction in the second eye that deviates 1.0 dioptres from target refraction 4 weeks postoperatively *Secondary outcome(s):* deviation of 0.5 dioptres from target refraction at 4 weeks postoperatively, visual acuity, complications, patient-reported outcome measures using with NEI-VFQ-25/Catquest/HUI-3/EQ-5D-5L questionnaires, Quality Adjusted Life Years, costs per participant, incremental cost-effectiveness ratios, budget impact *Follow-up length:* 3 months *Follow-up time points:* 1 week, 4 weeks, 3 months
Starting date	1 September 2018
Contact information	Maastricht University Medical Center (MUMC+), Maastricht, Limburg, Netherlands, 6229 HX Contact: Lindsay Spekreijse, MD; 433875404 ext 0031, lindsay.spekreijse@mumc.nl Contact: Frank van den Biggelaar, 433877344 ext 0031, f.vandenbiggelaar@mumc.nl
Notes	Sponsors and Collaborators: Maastricht University Medical Center; ZonMw: The Netherlands Organisation for Health Research and Development

DSBCS: delayed sequential bilateral cataract surgery; EQ-5D-5L: EuroQol-5 Dimension 5 levels; HUI-3: Health Utilities Index – 3; IOL: intraocular lens; ISBCS: immediate sequential bilateral cataract surgery; NEI-VFQ-25: National Eye Institute Visual Function Questionnaire – 25; NR: not reported.

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 Endophthalmitis – randomised controlled trials (RCTs) (effect of assignment)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sarikkola 2011	~	✓	✓	✓	~	~
Serrano-Aguilar 2012	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.2 Endophthalmitis – RCTs (effect of adherence)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sarikkola 2011	~	✗	✓	✓	~	✗
Serrano-Aguilar 2012	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.6 Refraction NOT within 1.0 dioptres of target (1–3 months after surgery) – RCTs (effect of assignment)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sarikkola 2011	~	✓	✓	✓	~	~

Risk of bias for analysis 1.10 Postoperative complications – RCTs (effect of assignment)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sarikkola 2011	~	✓	✓	✓	~	~
Serrano-Aguilar 2012	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.12 Patient-reported outcome measures (PROMs) – RCTs (effect of assignment)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sarikkola 2011	~	✓	✗	✗	~	✗

	Bias					
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Serrano-Aguilar 2012						

DATA AND ANALYSES

Comparison 1. Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Endophthalmitis – randomised controlled trials (RCTs) (effect of assignment)	2	2613	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Endophthalmitis – RCTs (effect of adherence)	2	2594	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Endophthalmitis – non-randomised studies (NRSs) (effect of assignment)	7	570322	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.32, 12.16]
1.4 Refraction NOT within 0.5 dioptres of target (1–3 months after surgery) – RCTs (effect of assignment)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.5 Refraction NOT within 0.5 dioptres of target (1–3 months after surgery) – NRSs (effect of assignment)	2	578	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.84, 1.83]
1.6 Refraction NOT within 1.0 dioptres of target (1–3 months after surgery) – RCTs (effect of assignment)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.7 Refraction NOT within 1.0 dioptres of target (1–3 months after surgery) – NRSs (effect of assignment)	3	946	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.60, 1.75]
1.8 Intraoperative complications – RCTs (effect of assignment)	2	2613	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.47, 1.21]
1.9 Intraoperative complications – NRSs (effect of assignment)	6	524567	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.07, 1.51]
1.10 Postoperative complications – RCTs (effect of assignment)	2	2610	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.52, 3.40]
1.11 Postoperative complications – NRSs (effect of assignment)	5	25739	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.47, 2.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12 Patient-reported outcome measures (PROMs) – RCTs (effect of assignment)	2	1297	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.19, 0.03]

Analysis 1.1. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 1: Endophthalmitis – randomised controlled trials (RCTs) (effect of assignment)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Sarikkola 2011 (1)	0	493	0	506		Not estimable		?	+	+	+	?	?
Serrano-Aguilar 2012 (1)	0	834	0	780		Not estimable		+	+	+	+	?	?
Total (95% CI)		**1327**		**1286**		**Not estimable**							
Total events:	0		0										
Heterogeneity: Not applicable													
Test for overall effect: Not applicable							Favours ISBCS Favours DSBCS						
Test for subgroup differences: Not applicable													

Footnotes
(1) Reported numbers are on eye level (both eyes of 1 participant).

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 2: Endophthalmitis – RCTs (effect of adherence)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Sarikkola 2011 (1)	0	480	0	500		Not estimable		?	-	+	+	?	-
Serrano-Aguilar 2012 (2)	0	834	0	780		Not estimable		+	+	+	+	?	?
Total (95% CI)		**1314**		**1280**		**Not estimable**							
Total events:	0		0										
Heterogeneity: Not applicable													
Test for overall effect: Not applicable							Favours ISBCS Favours DSBCS						
Test for subgroup differences: Not applicable													

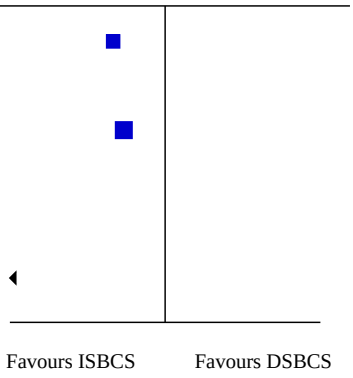
Footnotes
(1) Reported numbers are on eye level (both eyes of 1 participant).
(2) Reported numbers are on eye level (both eyes of 1 participant). Numbers per protocol were equal to those of intention to treat.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 3: Endophthalmitis – non-randomised studies (NRSs) (effect of assignment)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Weight	Risk Ratio M-H, Random, 95% CI
Buchan 2020 (1)	0	2146	53	496682	42.6%	2.16 [0.13 , 35.00]
Cholevik 2015 (1)	0	100	0	100		Not estimable
Chung 2009 (1)	0	188	0	200		Not estimable
Herrinton 2017 (1)	1	10494	2	38736	57.4%	1.85 [0.17 , 20.35]
Kim 2015 (1)	0	924	0	20216		Not estimable
Nassiri 2009 (2)	0	140	0	228		Not estimable
Rush 2015 (3)	0	84	0	84		Not estimable
Total (95% CI)		**14076**		**556246**	**100.0%**	**1.97 [0.32 , 12.16]**
Total events:	1		55			

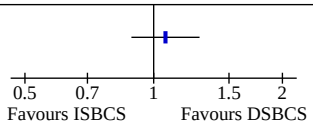
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.46)
Test for subgroup differences: Not applicable



Footnotes
(1) Reported numbers are on eye level (both eyes of 1 participant). Unadjusted for confounders.
(2) Reported on eye level (both eyes of 1 participant). Unadjusted effect (but important confounders as exclusion criteria).
(3) Reported on eye level (both eyes of 1 participant). Unadjusted effect (except exclusion immunocompromised participants).

Analysis 1.4. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 4: Refraction NOT within 0.5 dioptres of target (1–3 months after surgery) – RCTs (effect of assignment)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Sarikkola 2011 (1)	160	488	152	494	1.07 [0.89 , 1.28]	?	+	+	+	?	?



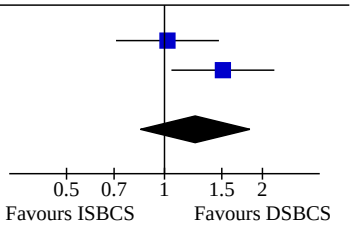
Footnotes
(1) Reported numbers are on eye level (both eyes of 1 participant).

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 5: Refraction NOT within 0.5 dioptres of target (1–3 months after surgery) – NRSs (effect of assignment)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Weight	Risk Ratio M-H, Random, 95% CI
Cholevik 2015 (1)	36	94	36	96	50.0%	1.02 [0.71 , 1.47]
Chung 2009 (1)	54	188	38	200	50.0%	1.51 [1.05 , 2.18]
Total (95% CI)		**282**		**296**	**100.0%**	**1.24 [0.84 , 1.83]**
Total events:	90		74			

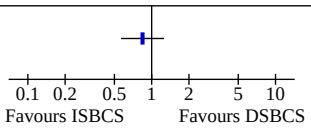
Heterogeneity: Tau² = 0.04; Chi² = 2.26, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Footnotes
(1) Reported numbers are on eye level (both eyes of 1 participant). Unadjusted for confounders.

Analysis 1.6. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 6: Refraction NOT within 1.0 dioptres of target (1–3 months after surgery) – RCTs (effect of assignment)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Sarikkola 2011 (1)	40	488	48	494	0.84 [0.57 , 1.26]	?	+	+	+	?	?



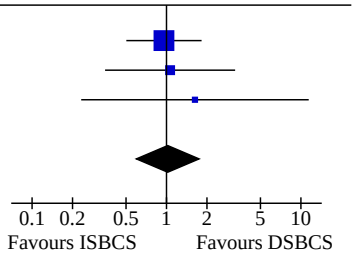
Footnotes
(1) Reported numbers are on eye level (both eyes of 1 participant).

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.7. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 7: Refraction NOT within 1.0 dioptres of target (1–3 months after surgery) – NRSs (effect of assignment)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Weight	Risk Ratio M-H, Random, 95% CI
Cholevik 2015 (1)	15	94	16	96	69.2%	0.96 [0.50 , 1.82]
Chung 2009 (1)	6	188	6	200	23.2%	1.06 [0.35 , 3.24]
Nassiri 2009 (2)	2	140	2	228	7.6%	1.63 [0.23 , 11.43]
Total (95% CI)		**422**		**524**	**100.0%**	**1.02 [0.60 , 1.75]**
Total events:	23		24			

Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable



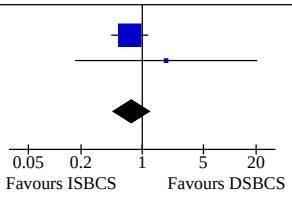
Footnotes

(1) Reported numbers are on eye level (both eyes of 1 participant). Unadjusted for confounders.
(2) Reported numbers are on eye level (both eyes of 1 participant). Unadjusted for confounders (e.g. biometry measurement techniques).

Analysis 1.8. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 8: Intraoperative complications – RCTs (effect of assignment)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Sarikkola 2011 (1)	26	493	37	506	96.1%	0.72 [0.44 , 1.17]	? + + + ? ?
Serrano-Aguilar 2012 (1)	2	834	1	780	3.9%	1.87 [0.17 , 20.59]	+ + + + ? ?
Total (95% CI)		**1327**		**1286**	**100.0%**	**0.75 [0.47 , 1.21]**	
Total events:	28		38				

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)
Test for subgroup differences: Not applicable



Footnotes

(1) Reported numbers are on eye level (both eyes of 1 participant).

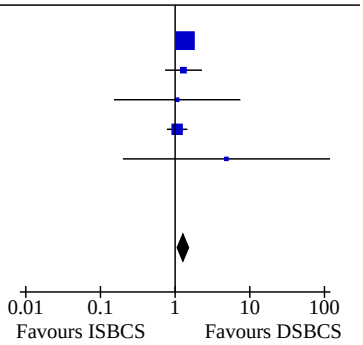
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.9. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 9: Intraoperative complications – NRSs (effect of assignment)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Weight	Risk Ratio M-H, Random, 95% CI
Buchan 2020 (1)	76	2146	12792	496682	60.3%	1.38 [1.10 , 1.72]
Cholevik 2015 (1)	22	100	17	100	9.1%	1.29 [0.73 , 2.29]
Chung 2009 (1)	2	188	2	200	0.8%	1.06 [0.15 , 7.48]
Herrinton 2017 (2)	49	5247	170	19368	29.5%	1.06 [0.78 , 1.46]
Nassiri 2009 (3)	1	140	0	228	0.3%	4.87 [0.20 , 118.78]
Rush 2015 (1)	0	84	0	84		Not estimable
Total (95% CI)		**7905**		**516662**	**100.0%**	**1.27 [1.07 , 1.51]**
Total events:	150		12981			

Heterogeneity: Tau² = 0.00; Chi² = 2.42, df = 4 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.72 (P = 0.006)
Test for subgroup differences: Not applicable



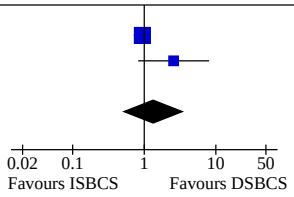
Footnotes

(1) Reported numbers are on eye level (both eyes of 1 participant). Unadjusted for confounders.
(2) Reported numbers are on participant level.
(3) Reported numbers are on eye level (both eyes of 1 participant). Unadjusted effect (but important confounders as exclusion criteria).

Analysis 1.10. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 10: Postoperative complications – RCTs (effect of assignment)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Sarikkola 2011 (1)	80	492	87	504	65.7%	0.94 [0.71 , 1.24]	? + + + ? ?
Serrano-Aguilar 2012 (1)	11	834	4	780	34.3%	2.57 [0.82 , 8.04]	+ + + + ? ?
Total (95% CI)		**1326**		**1284**	**100.0%**	**1.33 [0.52 , 3.40]**	
Total events:	91		91				

Heterogeneity: Tau² = 0.33; Chi² = 2.84, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



Footnotes

(1) Reported numbers are on eye level (both eyes of 1 participant).

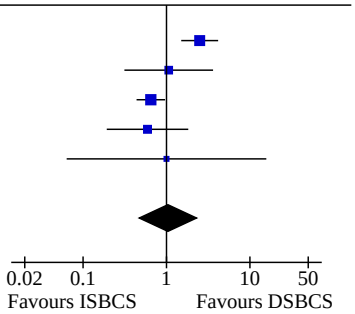
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.11. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 11: Postoperative complications – NRSs (effect of assignment)

Study or Subgroup	ISBCS Events	ISBCS Total	DSBCS Events	DSBCS Total	Weight	Risk Ratio M-H, Random, 95% CI
Cholevik 2015 (1)	40	100	16	100	27.6%	2.50 [1.50 , 4.16]
Chung 2009 (1)	5	188	5	200	17.8%	1.06 [0.31 , 3.62]
Herrinton 2017 (2)	29	5247	165	19368	29.0%	0.65 [0.44 , 0.96]
Nassiri 2009 (3)	4	140	11	228	19.1%	0.59 [0.19 , 1.82]
Rush 2015 (1)	1	84	1	84	6.5%	1.00 [0.06 , 15.73]
Total (95% CI)		**5759**		**19980**	**100.0%**	**1.04 [0.47 , 2.29]**
Total events:	79		198			

Heterogeneity: Tau² = 0.52; Chi² = 18.10, df = 4 (P = 0.001); I² = 78%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable



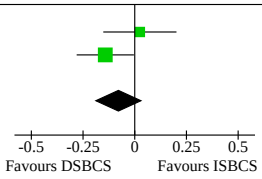
Footnotes

(1) Reported numbers are on eye level (both eyes of 1 participant). Unadjusted for confounders.
(2) Reported numbers are on participant level (events represent macular oedema only). Unadjusted for confounders.
(3) Reported on eye level (both eyes of 1 participant). Unadjusted effect (but important confounders as exclusion criteria).

Analysis 1.12. Comparison 1: Immediate sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS), Outcome 12: Patient-reported outcome measures (PROMs) – RCTs (effect of assignment)

Study or Subgroup	ISBCS Mean	ISBCS SD	ISBCS Total	DSBCS Mean	DSBCS SD	DSBCS Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Sarikkola 2011 (1)	24.3	21	243	23.8	19.2	248	37.9%	0.02 [-0.15 , 0.20]	? + - - ? -
Serrano-Aguilar 2012 (1)	26.7	22.4	417	29.8	21	389	62.1%	-0.14 [-0.28 , -0.00]	+ + + - ? -
Total (95% CI)			**660**			**637**	**100.0%**	**-0.08 [-0.19 , 0.03]**	

Heterogeneity: Chi² = 2.13, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable



Footnotes

(1) Reported numbers are on participant level.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Risk of bias in economic evaluations: CHEERS Checklist completed for all selected economical evaluations

CHEERS checklist			Reported in Study					
Section/item	**Item No**	**Recommendation**	**Leivo 2011**	**O'Brien 2010**	**Rush 2015**	**Lundstrom 2009**	**Malvankar-Mehta 2013**	**Neel 2014a**
Title and abstract								
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	No, page 1003	Yes, page 596	No	Yes, page 33	No	Yes, page 1282
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Yes, page 1003	Yes, page 596	Yes, page 732	No	Yes, page 482	Yes, page 1282
Introduction								
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Yes, page 1003	Yes, pages 596–597	Yes, pages 732 and 733	Yes, page 33	Yes, pages 482–484	Yes, page 1283
Methods								
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes, page 1004	No	Yes, page 733	No, page 34	No	No
Setting and location	5	State relevant aspect s of the system(s) in which the decision(s) need(s) to be made.	No	Yes, pages 596–597	Yes, page 733	No	No	Yes, page 1283
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes, page 1004	Yes, page 597	Yes, page 734	No	Yes, page 484	Yes, pages 1283–1284

Table 1. Risk of bias in economic evaluations: CHEERS Checklist completed for all selected economical evaluations *(Continued)*

Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Yes, page 1004	Yes, page 597	Yes, pages 733 and 734	Yes, pages 33–34	Yes, page 484	Yes, page 1283
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes, page 1004	Yes, page 597	Yes, page 734	No	No	No
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	NA	NA	NA (< 1 year)	No	No, pages 486–487 (incorrectly applied)	NA
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Yes, page 1004	NA	NA (cost analysis only)	Yes, page 34	Yes, page 486	NA
Measurement of effectiveness	11a	Single study-based estimates: describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Yes, page 1004	NA	Yes, pages 733 and 734	No, page 34	NA	NA
	11b	Synthesis-based estimates: describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA	NA	NA	NA	Yes, page 484	NA
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA	NA	NA	NA	No	NA

Table 1. Risk of bias in economic evaluations: CHEERS Checklist completed for all selected economical evaluations *(Continued)*

Estimating resources and costs	13a	Single study-based economic evaluation: describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Yes, page 1004	Yes, pages 597–598	Yes, page 734	NA	NA	NA
	13b	Model-based economic evaluation: describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA	NA	NA	Yes	Yes, pages 484–486	Yes, pages 1283–1284
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Yes, page 1004	No	No	No	No	Yes, pages 1283–1284
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	NA	NA	NA	NA	Yes, pages 483–484	NA
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	NA	NA	NA	NA	Yes, pages 484–486	NA
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	NA	NA	No	No	No	NA

Table 1. Risk of bias in economic evaluations: CHEERS Checklist completed for all selected economical evaluations *(Continued)*

Results								
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	No	No	Yes, page 736	No	Yes, pages 484–486	No
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Yes, page 1005	Yes, page 598	Yes, page 736	Yes, pages 35–36	Yes, pages 483 and 487	Yes, pages 1285–1286
Characterising uncertainty	20a	Single study-based economic evaluation: describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	No	No	No	NA	NA	NA
	20b	Model-based economic evaluation: describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	NA	NA	NA	No	Yes, page 487	No
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of participants with different baseline characteristics or other observed variability in effects that are not reducible by more information.	No	No	NA	No	No	No
Discussion								
Study findings, limitations, generalisability,	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Yes, pages 1006–1008	Yes, pages 598–600	No	Yes, pages 36–37	Yes, pages 487–488	Yes, pages 1286–1287

Table 1. Risk of bias in economic evaluations: CHEERS Checklist completed for all selected economical evaluations *(Continued)*

and current knowledge								
Other								
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	No	No	No	Yes, page 37	Yes, page 488	No
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes, page 1003	Yes, page 600	Yes, page 732	No	Yes, page 488	Yes, page 1287

Checklist completed as a consensus table (by RWPS and LSS).
NA: not available/applicable.

Table 2. Risk of bias in economic evaluations: CHEC-list completed for all applicable studies

CHEC-list		Study					
		Leivo 2011		O'Brien 2010		Rush 2015	
No	**Item**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
1.	Is the study population clearly described?	X	—	—	X	X	—
2.	Are competing alternatives clearly described?	X	—	X	—	X	—
3.	Is a well-defined research question posed in answerable form?	X	—	X	—	—	X
4.	Is the economic study design appropriate to the stated objective?	X	—	X	—	—	X
5.	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	X	—	—	X	X	—

Table 2. Risk of bias in economic evaluations: CHEC-list completed for all applicable studies *(Continued)*

6.	Is the actual perspective chosen appropriate?	X	—	—	X	X	—
7.	Are all important and relevant costs for each alternative identified?	X	—	X	—	—	X
8.	Are all costs measured appropriately in physical units?	X	—	—	X	—	X
9.	Are costs valued appropriately?	X	—	—	X	—	X
10.	Are all important and relevant outcomes for each alternative identified?	—	X	—	X	—	X
11.	Are all outcomes measured appropriately?	X	—	—	X	—	X
12.	Are outcomes valued appropriately?	—	X	—	X	—	X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	—	X	—	X	—	X
14.	Are all future costs and outcomes discounted appropriately?	X	—	—	X	—	X
15.	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	—	X	—	X	—	X
16.	Do the conclusions follow from the data reported?	X	—	X	—	X	—
17.	Does the study discuss the generalisability of the results to other settings and patient/client groups?	X	—	X	—	—	X
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X	—	X	—	X	—
19.	Are ethical and distributional issues discussed appropriately?	X	—	X	—	—	X

Checklist completed as a consensus table (by RWPS and LSS).

Table 3. Risk of bias in economic evaluations: NICE Checklist completed for all applicable studies

NICE Item	Study					
	Lundstrom 2009		Malvankar-Mehta 2013		Neel 2014a	
Section 1: applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) This checklist should be used first to filter out irrelevant studies.	**Yes/partly/ no/unclear/ NA**	**Comments**	**Yes/partly/ no/unclear/ NA**	**Comments**	**Yes/partly/ no/unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Unclear	No description of participant characteristics.	Unclear	—	Unclear	—
1.2 Are the interventions appropriate for the review question?	Yes	—	Yes	—	Yes	—
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	NA	—	NA	—	NA	—
1.4 Is the perspective for costs appropriate for the review question?	Unclear	Perspective not clearly stated.	Yes	—	Yes	—
1.5 Is the perspective for outcomes appropriate for the review question?	Partly	QALYs are not included.	Yes	—	NA	—
1.6 Are all future costs and outcomes discounted appropriately?	NA	< 1 year	No	Discounting has been applied in an improper manner.	NA	< 1 year
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	No	No QALYs are calculated/used. The measure of effects used includes a capability index (data on activities collected through interviews with patients).	Partly	QALYs were included in the model, but not elicited using preferred methods.	No	No QALYs are calculated.

Table 3. Risk of bias in economic evaluations: NICE Checklist completed for all applicable studies *(Continued)*

1.8 **Overall judgement:** there is no need to use section 2 of the checklist if the study is considered 'not applicable'.	Partially applicable (healthcare/hospital costs)		Partially applicable. The study used QALYs and costs from a third-party payer perspective, but QALYs were not measured using preferred methods.		Partially applicable	
Other comments:	NA		NA		NA	
Section 2: study limitations (the level of methodological quality): this checklist should be used once it has been decided that the study is sufficiently applicable to the context of the guideline.	**Yes/ partly/ no/ unclear/ NA**	**Comments**	**Yes/ partly/ no/ unclear/ NA**	**Comments**	**Yes/ partly/ no/ unclear/ NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Partly	Postoperative complications costs/impact not included.	Yes	—	NA	—
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Unclear	Time horizon not clearly described. Unclear whether time horizon is the same for effects and costs.	Unclear	Time horizon not clearly described. Unclear whether time horizon is the same for effects and costs.	No	Only costs are included that are incurred on the day of the surgery, not postoperative costs of visits or treatment of complications.
2.3 Are all important and relevant outcomes included?	No	Not all relevant outcomes are included.	Yes	—	NA	—
2.4 Are the estimates of baseline outcomes from the best available source?	NA	Baseline outcomes not relevant for the current study.	Yes	—	NA	—
2.5 Are the estimates of relative intervention effects from the best available source?	NA	Estimates of relative intervention effects not relevant for the current study.	No	Utilities are based on a single study, which modelled utilities based on best-corrected visual acuity of the better seeing eye.	NA	—
2.6 Are all important and relevant costs included?	No	Does not include all relevant costs for a health-	No	While most important cost categories were included to determine costs from a third-party	Partly	Only costs are included that are incurred on

Table 3. Risk of bias in economic evaluations: NICE Checklist completed for all applicable studies *(Continued)*

		care or societal perspective (productivity losses, homecare).		perspective, errors were made in the calculation of costs. The study extracted surgical costs of DSBCS and ISBCS from a previous cost study (O'Brien 2010). In that previous study, costs were reported for 1 eye in both cases. In the model-based cost-utility analyses by Malvankar-Mehta 2013, the cost of DSBCS was correctly doubled to account for both eyes, but the cost for ISBCS was erroneously included for 1 eye only. When evaluating the decision tree, costs of ISBCS are less than half of those of DSBCS (ISBCS without complications: 1304 in total (1059 surgical costs and 245.38 follow-up and medication) and for DSBCS without complications: 3280 in total (2 times 1566 surgical costs and 147.69 follow-up and medication)).		the day of the surgery, not postoperative costs of visits or treatment of complications.
2.7 Are the estimates of resource use from the best available source?	Partly	Not derived from systematic review, but from a single study.	Partly	Units of resource use were derived from a previous study in the same healthcare system, and from the hospital where this study was conducted at, but this was not a systematic review.	Partly	Estimated on resource use were derived from a single surgical centre.
2.8 Are the unit costs of resources from the best available source?	Partly	Not derived from systematic review, but from a single study.	Partly	Unit costs were derived from a previous study in the same healthcare system, and from the hospital where this study was conducted at, but this was not a systematic review.	Partly	Costs were largely based on reimbursement prices.
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	No	No ICERs calculated	Yes	—	NA	—
2.10 Are all important parameters whose values are	No	No sensitivity analysis	Partly	Not all input parameters in the model were	No	No sensitivity analyses

Table 3. Risk of bias in economic evaluations: NICE Checklist completed for all applicable studies *(Continued)*

uncertain subjected to appropriate sensitivity analysis?		has been performed.		explored in the sensitivity analysis.		were performed.
2.11 Has no potential financial conflict of interest been declared?	Unclear	—	Yes	—	Yes	—
2.12 **Overall assessment**	Potentially serious limitations		Very serious limitations		Potentially serious limitations	
Other comments	NA		The study made significant errors in the calculation of costs. In addition, discounting was not applied in a correct manner. Consequently, the results of this study can be considered invalid.		Costs were based on reimbursement prices, the time horizon was limited to the day of surgery, no effectiveness parameters were included in the analysis.	

Checklist completed as a consensus table (by RWPS and LSS).
DSBCS: delayed sequential bilateral cataract surgery; ICER: incremental cost-effectiveness ratio; ISBCS: immediate sequential bilateral cataract surgery; QALY: quality-adjusted life year.

Table 4. ROBINS-I assessments for ISBCS versus DSBCS in people with bilateral age-related cataracts: complications (endophthalmitis, intraoperative, postoperative) up to three months after surgery (effect of assignment)

Study	Bias due to confounding	Bias in classification of interventions	Bias in selection of participants into the study	Bias due to deviations from the intended intervention (assignment)	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Buchan 2020	Serious	Serious	Moderate	Low	Serious	Moderate	Serious	Serious
Rationale for judgement	The authors did not control for all potential confounders relevant to the risk of complications. There were significant baseline differences (ISBCS more participants with high myopia mature cataract, and inherited optic CNS disease; lower mean age in ISBCS group). Furthermore, significantly more participants in the ISBCS group underwent general anaesthesia (58.7%).	There is some risk of immortal time bias. There is no information on whether participants in the ISBCS group were converted to the DSBCS group.	There is some risk of immortal time bias. Furthermore, it is unclear whether selection into the study could be related to the intervention and outcomes (complication, refraction). However, this is unlikely, since data are entered at the start of intervention in a database.	Participants did not choose the intervention in an experimental setting. Data was collected in a national database (regular practice).	No information is provided on completeness of data or on reasons for missingness.	No information was provided on the methods for measurement of the outcome. Outcome assessors were probably not blinded to the intervention received. However, because of the nature of the outcome (complications), assessment is less likely to have been influences by knowledge of the intervention.	There is no predetermined analysis plan available.	Overall serious risk of bias, because 4/7 domains were serious.
Cholevik 2015	Serious	Serious	Serious	Low	Low	Serious	Serious	Serious
Rationale for judgement	The authors did not control for potential confounders. There is a baseline imbalance in systemic and ocu-	There is some potential for immortal time bias, since 2 participants initially planned for ISBCS were	Since the study was retrospective, it was not possible to know whether participant selection was free from bias. Both intervention and out-	Since the study was not undertaken in an experimental setting, there is a low risk of deviation from in-	Data on complications was probably available for all, or nearly all, participants and	It is unclear how data collection were performed. Since ISBCS participants had ≥ 1 additional follow-up examination (1 day after surgery) compared	There is no predetermined analysis plan available.	Overall serious risk of bias, because 5/7 domains were at se-

Table 4. ROBINS-I assessments for ISBCS versus DSBCS in people with bilateral age-related cataracts: complications (endophthalmitis, intraoperative, postoperative) up to three months after surgery (effect of assignment) *(Continued)*

	lar comorbidities between groups, favouring the ISBCS group.	placed in the DSBCS group after postponing the second eye. Since postponement was due to complications, this might favour the outcomes for the ISBCS group.	come could be related to the selection process.	tended intervention.	it is unlikely that missingness of this outcome is related to the true value of the outcome, since complications are likely to be registered.	to DSBCS-treated participants, this created an extra opportunity for identifying adverse events in ISBCS-treated participants.		rious risk of bias.
Chung 2009	Serious	Serious	Moderate	Low	Moderate	Low	Serious	Serious
Rationale for judgement	The authors did not control for all potential confounders. Ocular comorbidities were excluded in equal numbers for both groups, but there was no information on the presence of potential risk factors for endophthalmitis or complications.	There is potential for immortal time bias. However, no switching between ISBCS and DSBCS groups was reported.	Additional exclusion of participants was done based on characteristics observed after the start of intervention (i.e. ocular comorbidities). However, exclusion numbers were comparable between groups.	Participants were allocated to a group based on preference and potential non-adherence to a certain intervention, or changes to this intervention, are most likely typical of routine care (not related to the experimental context).	Cases with missing data were excluded from the analysis. However, the number of exclusions and reasons for exclusion were comparable between groups.	Measurements were performed at predefined time points and did not differ between groups. Because of the nature of the outcome (complications), assessment is unlikely to have been influenced by knowledge of the intervention.	There is no predetermined analysis plan available.	Overall serious risk of bias, because 3 domains were at serious risk of bias.
Herrinton 2017	Serious	Serious	Moderate	Low	Low	Low	Serious	Serious
Rationale for judgement	The authors did not control for potential confounders and there were imbalances in several ocular comor-	There is some potential for immortal time bias, since 25 participants (0.7%) initially planned for ISBCS were	Since the study was retrospective, it was not possible to know whether participant selection was free from bias. Both intervention and outcome could be relat-	The study was not undertaken in an experimental context.	Data on complications was probably available for all, or nearly all, participants (continuity of	Information on complications was extracted from medical records. Considering the nature of the outcome (complications), it is unlikely that assessment was influ-	There is no predetermined analysis plan available.	Overall serious risk of bias, because 3 domains were at serious risk of bias.

Table 4. ROBINS-I assessments for ISBCS versus DSBCS in people with bilateral age-related cataracts: complications (endophthalmitis, intraoperative, postoperative) up to three months after surgery (effect of assignment) *(Continued)*

	bidities at baseline.	converted to the DSBCS group after complications.	ed to the selection process.		membership 95% in the year following surgery).	enced by knowledge of the intervention received.		
Kim 2015	Serious	Serious	Serious	Low	Serious	Low	Serious	Serious
Rationale for judgement	The authors did not control for all potential confounders. Ocular comorbidities were excluded but this was not further specified.	There is some potential for immortal time bias. There is no information on whether participants in the ISBCS group were converted to the DSBCS group.	Since the study was retrospective, it was not possible to know whether participant selection was free from bias. Both intervention and outcome could be related to the selection process.	The study was not undertaken in an experimental context.	No information on completeness of data or on reasons for missingness.	Information on complications was extracted from medical records. Considering the nature of the outcome (complications), it is unlikely that assessment was influenced by knowledge of the intervention received.	There is no predetermined analysis plan available.	Overall serious risk of bias, because 5/7 domains were at serious risk of bias.
Nassiri 2009	Low	Serious	Moderate	Low	Moderate	Low	Serious	Serious
Rationale for judgement	Important confounders for increased complication risk were listed as exclusion criteria.	There is some risk of immortal time bias. There is no information on whether participants in the ISBCS group were converted to the DSBCS group.	Most important risk factors that could influence selection were accounted for in the exclusion criteria. However, selection into the study could still be related to the intervention and outcomes (complication, refraction).	Participants were allocated to a group based on preference and potential non-adherence to a certain intervention, or changes to this intervention, are most likely typical of routine care (not related to the experimental context).	Data were not complete (missing data on 12.5% of ISBCS and 18.6% of DSBCS-treated participants due to lost to follow-up). There was no information on reasons for lost to follow-up. However, it is unlikely that missingness was related to the true val-	Because of the nature of the outcome, assessment is unlikely to have been influenced by knowledge of the intervention.	There is no predetermined analysis plan available.	Overall serious risk of bias, because 2 domains were at serious risk of bias.

Table 4. ROBINS-I assessments for ISBCS versus DSBCS in people with bilateral age-related cataracts: complications (endophthalmitis, intraoperative, postoperative) up to three months after surgery (effect of assignment) *(Continued)*

					ue of the outcome.			
Rush 2015	Serious	Serious	Moderate	Low	Serious	Low	Serious	Serious
Rationale for judgement	The authors did not control for all potential confounders relevant to the risk of complications.	There is some risk of immortal time bias. There is no information on whether participants in the ISBCS group were converted to the DSBCS group.	Most important risk factors that could influence selection were accounted for in the exclusion criteria. However, selection into the study could still be related to the intervention and outcomes (complication, refraction).	Participants were allocated to a group based on preference and potential non-adherence to a certain intervention, or changes to this intervention, are most likely typical of routine care (not related to the experimental context).	No information on completeness of data or on reasons for missingness.	Measurements were performed at predefined time points and did not differ between groups. Because of the nature of the outcome (complications), assessment is unlikely to have been influences by knowledge of the intervention.	There is no predetermined analysis plan available.	Overall serious risk of bias, because 4/7 domains were at serious risk of bias.

DSBCS: delayed sequential bilateral cataract surgery; CNS: central nervous system; ISBCS: immediate sequential bilateral cataract surgery.

Table 5. ROBINS-I assessments for ISBCS versus DSBCS in people with bilateral age-related cataracts: refraction one to three months after surgery (effect of assignment)

Study	Bias due to confounding	Bias in classification of interventions	Bias in selection of participants into the study	Bias due to deviations from the intended intervention (assignment)	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Cholevik 2015	Serious	Serious	Serious	Low	Low	Low	Serious	Serious
Rationale for judgement	The authors did not control for potential confounders.	The authors did not control for potential confounders. Participants with	Since the study was retrospective, it was not possible to know whether participant selection was free	Since the study was not undertaken in an experimental setting, there is a	Some participants were missing, but completeness of refraction data at base-	It is unclear how data collection was performed. Refraction is mea-	There is no predetermined analysis	Overall serious risk of bias, because 4/7 domains

Table 5. ROBINS-I assessments for ISBCS versus DSBCS in people with bilateral age-related cataracts: refraction one to three months after surgery (effect of assignment) *(Continued)*

	There is a baseline imbalance in axial length and ocular comorbidities between groups.	extreme axial lengths were included in the study. No information is provided on the distribution of axial lengths within groups or on differences between groups.	from bias. Both intervention and outcome could be related to the selection process.	low risk of deviation from intended intervention.	line and at 3 months' follow-up is ≥ 91%.	sured at the same time points for both groups.	plan available.	were serious.
Chung 2009	Serious	Serious	Moderate	Low	Moderate	Low	Serious	Serious
Rationale for judgement	The authors did not control for all potential confounders. No data on potential differences in baseline characteristic on biometry (e.g. axial length) were presented.	There is potential for immortal time bias. However, no switching between ISBCS and DSBCS groups was reported.	Additional exclusion of patients was done based on characteristics observed after the start of intervention (i.e. ocular comorbidities). However, exclusion numbers were comparable between groups.	Participants were allocated to a group based on preference and potential non-adherence to a certain intervention, or changes to this intervention, are most likely typical of routine care (not related to the experimental context).	Cases with missing data were excluded from the analysis. However, the number of exclusions and reasons for exclusion were comparable between groups.	Measurements were performed at predefined time points and did not differ between groups. Because of the nature of the outcome, assessment is unlikely to have been influenced by knowledge of the intervention.	There is no predetermined analysis plan available.	Overall serious risk of bias, because 3 domains were at serious risk of bias.
Herrinton 2017	Serious	Serious	Moderate	Low	Moderate	Critical	Serious	Critical
Rationale for judgement	The authors did not control for potential confounders.	There is some potential for immortal time bias, since 25 participants (0.7%) initially planned for ISBCS were converted to the DSBCS group	Since the study was retrospective, it was not possible to know whether participant selection was free from bias. Both intervention and outcome could be related to the selection process.	The study was not undertaken in an experimental context.	Data on refractive outcomes was available for 94–95% of participants with information on BCDVA (only available for 68–71% of participants). However, it is unlikely that reasons for exclusion from	There was no availability of data on preoperative target. So, refractive error was measured using emmetropia as a target, excluding cases that	There is no predetermined analysis plan available.	Overall critical risk of bias, because 1 domain was at critical risk of bias.

Table 5. ROBINS-I assessments for ISBCS versus DSBCS in people with bilateral age-related cataracts: refraction one to three months after surgery (effect of assignment) *(Continued)*

		after complications.			the analysis are related to the true value of the outcome.	deviated from emmetropia > 2 dioptres.		
Nassiri 2009	Serious	Serious	Moderate	Low	Moderate	Low	Serious	Serious
Rationale for judgement	The authors did not control for potential confounders and no information is provided on potential differences in baseline characteristics between groups (e.g. biometric data)	There is some risk of immortal time bias. There is no information on whether participants in the ISBCS group were converted to the DSBCS group.	Most important risk factors that could influence selection were accounted for in the exclusion criteria. However, selection into the study could still be related to the intervention and outcomes (complication, refraction).	Participants were allocated to a group based on preference and potential non-adherence to a certain intervention, or changes to this intervention, are most likely typical of routine care (not related to the experimental context).	Data were not complete (missing data on 12.5% of ISBCS and 18.6% of DSBCS-treated participants due to lost to follow-up). There was no information on reasons for lost to follow-up. It is not very likely that missingness was related to the true value of the outcome since percentages were comparable between groups.	Because of the nature of the outcome, assessment is unlikely to have been influenced by knowledge of the intervention.	There is no predetermined analysis plan available.	Overall serious risk of bias, because 3 domains were at serious risk of bias.

DSBCS: delayed sequential bilateral cataract surgery; BCDVA: best-corrected distance visual acuity; ISBCS: immediate sequential bilateral cataract surgery.

Table 6. RoB 2 assessment for ISBCS versus DSBCS in people with bilateral age-related cataracts: best-corrected distance visual acuity (BCDVA) (effect of assignment)

Study	Risk of bias arising from the randomisation process	Bias due to deviations from the intended intervention (assignment)	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Sarikkola 2011	Some concerns	Low	Low	Low	Some concerns	Some concerns
Rationale for judgement	Randomisation was achieved using sealed envelopes. No further information is provided on the randomisation process (i.e. numbering and sealing of envelopes).	Blinding was not possible due to the nature of the study. Some participants in both study groups had second-eye surgery deferred or cancelled, which would also happen outside the trial context. No deviations were reported that were presumably related to the trial context.	Completion of data up to 1 month after second-eye surgery was 96.8%.	The same methods were used for both study groups. It was not indicated whether the outcome measurement was standardised.	No information provided.	Overall some concerns, because 2 domains had some concerns with regard to risk of bias.
Serrano-Aguilar 2012	Low	Low	Low	Some concerns	Some concerns	Some concerns
Rationale for judgement	A computer-generated randomisation sequence was used for participant allocation.	Blinding not possible due to the nature of the study. However, all participants received their allocated treatment and an ITT analysis was performed.	Outcome data at 1 month after surgery was available for nearly all participants. Only 1 participant was lost to follow-up.	Both surgeons and participants were aware of the intervention received. It is unclear whether outcome assessors were aware of the intervention received. Visual acuity is a subjective measurement that could have been affected by awareness of treatment allocation to a small extent.	No information provided.	Overall some concerns, because 2 domains had some concerns with regard to risk of bias.

DSBCS: delayed sequential bilateral cataract surgery; ISBCS: immediate sequential bilateral cataract surgery; ITT: intention-to-treat.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Cataract] explode all trees
#2 MeSH descriptor: [Cataract Extraction] this term only
#3 MeSH descriptor: [Phacoemulsification] this term only
#4 cataract*
#5 phaco* or phako*
#6 MeSH descriptor: [Lens Implantation, Intraocular] this term only
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 (immediate* or delay*) near/2 bilateral cataract*
#9 (immediate* or delay*) near/2 sequential cataract*

#10 (immediate* or delay*) near/2 (bilateral phaco* or bilateral phako*)
#11 (immediate* or delay*) near/2 (sequential phaco* or sequential phako*)
#12 ISBCS or DSBCS
#13 first eye near/1 cataract*
#14 second eye near/1 cataract*
#15 fellow eye near/1 cataract*
#16 simultaneous near/2 (phaco* or phako* or cataract*)
#17 bilateral near/2 (phaco* or phako* or endophthalmitis)
#18 bilateral near/2 (cataract* surg* or cataract* extract* or cataract* remov*)
#19 sequential near/2 (cataract* surg* or cataract* extract* or cataract* remov*)
#20 same day near/2 (phaco* or phako* or cataract* or surg*)
#21 SBCS
#22 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 #7 and #22

Appendix 2. MEDLINE Ovid search strategy

1. exp Cataract/
2. Cataract Extraction/
3. Phacoemulsification/
4. cataract$.tw.
5. (phaco$ or phako$).tw.
6. Lens Implantation, Intraocular/
7. or/1-6
8. ((immediate$ or delay$) adj2 bilateral cataract$).tw.
9. ((immediate$ or delay$) adj2 sequential cataract$).tw.
10. ((immediate$ or delay$) adj2 (bilateral phaco$ or bilateral phako$)).tw.
11. ((immediate$ or delay$) adj2 (sequential phaco$ or sequential phako$)).tw.
12. (ISBCS or DSBCS).tw.
13. (first eye adj1 cataract$).tw.
14. (second eye adj1 cataract$).tw.
15. (fellow eye adj1 cataract$).tw.
16. (simultaneous adj2 (phaco$ or phako$ or cataract$)).tw.
17. (bilateral adj2 (phaco$ or phako$ or endophthalmitis)).tw.
18. (bilateral adj2 (cataract$ surg$ or cataract$ extract$ or cataract$ remov$)).tw.
19. (sequential adj2 (cataract$ surg$ or cataract$ extract$ or cataract$ remov$)).tw.
20. (same day adj2 (phaco$ or phako$ or cataract$ or surg$)).tw.
21. SBCS.tw.
22. or/8-21
23. 7 and 22

Appendix 3. MEDLINE Ovid economics search strategy

1. Economics/
2. exp "costs and cost analysis"/
3. Economics, Dental/
4. exp economics, hospital/
5. Economics, Medical/
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
9. (expenditure$ not energy).ti,ab.
10. value for money.ti,ab.
11. budget$.ti,ab.
12. or/1-11
13. ((energy or oxygen) adj cost).ti,ab.
14. (metabolic adj cost).ti,ab.
15. ((energy or oxygen) adj expenditure).ti,ab.
16. or/13-15
17. 12 not 16
18. letter.pt.
19. editorial.pt.
20. historical article.pt.

21. or/18-20
22. 17 not 21
23. exp animals/ not humans/
24. 22 not 23
25. bmj.jn.
26. "cochrane database of systematic reviews".jn.
27. health technology assessment winchester england.jn.
28. or/25-27
29. 24 not 28
30. Cataract Extraction/
31. Phacoemulsification/
32. (phaco$ or phako$).tw.
33. Lens Implantation, Intraocular/
34. ((extract$ or aspirat$ or operat$ or remov$ or surg$ or excis$ or implant$) adj3 cataract$).tw.
35. ((extract$ or aspirat$ or operat$ or remov$ or surg$ or excis$ or implant$) adj3 lens$).tw.
36. or/30-35
37. 29 and 36

Appendix 4. Embase Ovid search strategy

1. exp Cataract/
2. Cataract Extraction/
3. Phacoemulsification/
4. cataract$.tw.
5. (phaco$ or phako$).tw.
6. lens implant/
7. lens implantation/
8. or/1-7
9. ((immediate$ or delay$) adj2 bilateral cataract$).tw.
10. ((immediate$ or delay$) adj2 sequential cataract$).tw.
11. ((immediate$ or delay$) adj2 (bilateral phaco$ or bilateral phako$)).tw.
12. ((immediate$ or delay$) adj2 (sequential phaco$ or sequential phako$)).tw.
13. (ISBCS or DSBCS).tw.
14. (first eye adj1 cataract$).tw.
15. (second eye adj1 cataract$).tw.
16. (fellow eye adj1 cataract$).tw.
17. (simultaneous adj2 (phaco$ or phako$ or cataract$)).tw.
18. (bilateral adj2 (phaco$ or phako$ or endophthalmitis)).tw.
19. (bilateral adj2 (cataract$ surg$ or cataract$ extract$ or cataract$ remov$)).tw.
20. (sequential adj2 (cataract$ surg$ or cataract$ extract$ or cataract$ remov$)).tw.
21. (same day adj2 (phaco$ or phako$ or cataract$ or surg$)).tw.
22. SBCS.tw.
23. or/9-22
24. 8 and 23

Appendix 5. Embase Ovid economics search strategy

1. Health Economics/
2. exp Economic Evaluation/
3. exp Health Care Cost/
4. pharmacoeconomics/
5. or/1-4
6. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
7. (expenditure$ not energy).ti,ab.
8. (value adj2 money).ti,ab.
9. budget$.ti,ab.
10. or/6-9
11. 5 or 10
12. letter.pt.
13. editorial.pt.
14. note.pt.
15. or/12-14
16. 11 not 15

17. (metabolic adj cost).ti,ab.
18. ((energy or oxygen) adj cost).ti,ab.
19. ((energy or oxygen) adj expenditure).ti,ab.
20. or/17-19
21. 16 not 20
22. animal/
23. exp animal experiment/
24. nonhuman/
25. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.
26. or/22-25
27. exp human/
28. human experiment/
29. or/27-28
30. 26 not (26 and 29)
31. 21 not 30
32. 0959-8146.is.
33. (1469-493X or 1366-5278).is.
34. 1756-1833.en.
35. or/32-34
36. 31 not 35
37. Conference abstract.pt.
38. 36 not 37
39. Cataract Extraction/
40. Phacoemulsification/
41. (phaco$ or phako$).tw.
42. lens implant/
43. lens implantation/
44. ((extract$ or aspirat$ or operat$ or remov$ or surg$ or excis$ or implant$) adj3 cataract$).tw.
45. ((extract$ or aspirat$ or operat$ or remov$ or surg$ or excis$ or implant$) adj3 lens$).tw.
46. or/39-45
47. 38 and 46

Appendix 6. ISRCTN search strategy

(cataract OR phacoemulsification) AND (immediate OR delay OR sequential OR simultaneous OR "first eye" OR "second eye")

Appendix 7. ClinicalTrials.gov search strategy

(cataract OR phacoemulsification) AND (immediate OR delay OR sequential OR simultaneous OR "first eye" OR "second eye")

Appendix 8. WHO ICTRP search strategy

(cataract OR phacoemulsification) AND (immediate OR delay OR sequential OR simultaneous OR first eye OR second eye)

Appendix 9. DARE and NHS EED on CRD Database

(cataract) AND (immediate) AND (delayed)

Appendix 10. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	• Parallel group RCT i.e. people randomised to treatment • Non-randomised controlled trial • Prospective cohort study • Retrospective cohort study • Cost-effectiveness study	Exclusions after randomisation Losses to follow-up Number randomised/analysed How were missing data handled? e.g. available case analysis, imputation methods

(Continued)

Eyes or unit of randomisation/unit of analysis	2 eyes included in study, both eyes received same treatment, Since people are randomly allocated, with the inclusion of both eyes to either intervention or comparator treatment, we will analyse this as clustered data, i.e. adjust for within-person correlation if possible, or present the outcome on patient level.	Reported power calculation (yes/no), if yes, sample size and power Unusual study design or issues
Participants		
Country		Setting
Total number of participants	This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed-up, please indicate.	Ethnic group Equivalence of baseline characteristics (yes/no)
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (N =) Comparator (N =)	Number of people randomised to this group	
Outcomes		
Primary and secondary outcomes as defined in study reports	List outcomes Adverse events reported (yes/no) Length of follow-up and intervals at which outcomes assessed	Planned and actual length of follow-up
Notes		
Trial Registration		
Date conducted	Specify dates of recruitment of participants (mm/yr to mm/yr)	Full study name: (if applicable)
Sources of funding		Reported subgroup analyses (Y/N)
Declaration of interest		Were trial investigators contacted?

HISTORY

Protocol first published: Issue 2, 2019

CONTRIBUTIONS OF AUTHORS

MMD: performed critical review and adjustments to all review sections.

LSS: screened titles and abstracts; assessed full-text copies for inclusion; screened economic evaluations against eligibility criteria; for economic evaluations, used an Excel template to collect study characteristics; assessed risk of bias, imported all data directly into Review Manager Web, and wrote the review manuscript.

BW: performed critical review of statistical sections, oversaw the statistical analyses.

JSAGS: performed critical review on clinical and methodological sections.

RWPS: screened titles and abstracts; assessed full-text copies for inclusion; screened economic evaluations against eligibility criteria; for economic evaluations, used an Excel template to collect study characteristics; assessed risk of bias; checked the accuracy of the data imported; performed critical review and adjustments to all review sections.

CDD: performed critical review on economic evaluations sections.

RMMAN: performed critical review on all review sections.

DECLARATIONS OF INTEREST

MMD: none.

LSS: none.

BW: none.

JSAGS: none.

RWPS: none.

CDD: none.

RMMAN: Abbot (Support), Alcon (Consultant, Lectures, Support), Asico (Consultant), Bausch & Lomb (Consultant), Carl-Zeiss (Support), CHIESI (Support), Gebauer (Support), Ophtec (Support), Human Optics (Support), Oculentis (Support), TheaPharma (Consultant)

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following aspects of the protocol were not implemented in the current review (e.g. because no studies, or few studies, were found) (Dickman 2019).

- We aimed to include registry studies, since these studies present outcomes of real-world practice and are expected to become important study designs in the future (Lauer 2013). However, such studies were not available for inclusion in the current review.
- We could not report the following outcomes, as no data were available: refraction within 0.5 dioptre and within 1.0 dioptre one week after surgery, visual acuity one week after surgery, mean change in visual acuity between baseline and one week, and mean change in visual acuity between baseline and one to three months after surgery.
- No additional correspondence with investigators regarding clarification of study eligibility for inclusion was required.
- We identified no studies with a registered completion date more than two years prior to our search. Therefore, we did not seek publications of such trials or contact study investigators to obtain published or unpublished data.
- For multi-arm studies, we planned to use data relevant to our intervention and comparator groups. If two groups contained relevant data, we planned to combine groups using the calculator in Review Manager (as recommended in Higgins 2011). However, no multi-arm studies were included in the current review.
- In the protocol, we described that we would present a pooled estimate for data from RCTs and NRSs if there was little or no heterogeneity by study design at the statistical or clinical level (Deeks 2017). However, as currently recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2021), we did not pool data from RCTs and NRSs.
- We did not calculate the mean difference (MD) and 95% CI for the continuous outcomes, visual acuity, and cost-effectiveness, since data were not available (cost-effectiveness) or too heterogeneous to allow comparison (visual acuity).
- We did not directly calculate costs to 2017 USD using the PPP for GDP, but first converted reported costs to a common year (2017) using the consumer price index as reported and advised by the OECD. Then, we converted the non-USD currency to 2017 USD using the PPP for GDP as reported by the OECD as described in our protocol.
- In case of multiple observations, due to repeated measurements for the same outcome (e.g. visual acuity, PROMs, refraction), we planned to define these as separate outcomes, depending on when the measurement was conducted, and perform separate analyses. However, this was not an issue in the current review.
- Since data were available for all eyes but not for first and second eyes separately for almost all included studies, we could not adjust for within-person correlation for outcomes measured on eye-level.
- We did not construct funnel plots or tests for asymmetry for assessment of publication bias, since there were fewer than 10 trials included in the meta-analyses (Higgins 2017).
- We could not identify sufficient trials and studies for comparison of the effect of treatment for ISBCS versus DSBCS in the subgroups reported in the review protocol.
- We could not perform sensitivity analyses to examine the impact of the following factors defined in the protocol: exclude high, serious or critical risk of bias (no studies left), exclude industry-funded studies (not applicable), use change from baseline instead of final value for visual acuity (data not available).
- We used Review Manager Web, the latest version of Review Manager 5.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cataract; *Cataract Extraction [adverse effects] [methods]; *Endophthalmitis; Lens Implantation, Intraocular [methods]; Visual Acuity

MeSH check words

Humans