National Institute for Health and Care Excellence

Final

Joint replacement (primary): hip, knee and shoulder

[F] Evidence review for anaesthesia for shoulder replacement

NICE guideline NG157

Intervention evidence review underpinning recommendation 1.3.3 in the NICE guideline

June 2020

Final

This evidence review was developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1.1 Review question: In adults having primary elective shoulder joint replacement, what is the most clinical and cost effective intraoperative anaesthetic approach?

1.2 Introduction

Elective primary shoulder replacement surgery is most commonly performed under a general anaesthetic. In recent years pain control post-surgery for patients has changed greatly. Pain control is important to aid recovery and additional options are discussed with patients pre-operatively and choices made about supplementary pain blocking procedures and post-operative analgesia (pain killers).

In addition to general anaesthesia, anaesthetists as routine now offer supplementary local anaesthetic interventions. Firstly a nerve block is an injection of anaesthetic into the nerves that supply the shoulder joint. The second option is local anaesthetic infiltration where a large volume of anaesthetic is injected it into the tissues around the operation site.

It is considered that such adjunct pre-emptive analgesic methods allow shoulder replacement patients to wake up pain free and get up and out of bed almost immediately post-operatively which can aid earlier discharge from hospital and less peri-operative morbidity.

Regional anaesthesia via inter-scalene nerve blocks under ultrasound guidance is now common practice in orthopaedic shoulder units for patients undergoing such surgery if there is no contraindication. These can be utilised instead or on top of general anaesthesia and do not benefit from augmentation with other nerve blocks or local anaesthetic infiltration.

This review seeks to determine the most clinically effective and cost-effective approach to anaesthesia for total shoulder replacement surgery.

1.3 PICO table

For full details see the review protocol in Appendix A:

Table 1: PICO characteristics of review question

Population	Adults having primary elective shoulder joint replacement
Interventions	• General anaesthesia • General anaesthesia with local infiltration analgesia (LIA) • General anaesthesia with regional anaesthesia (ultrasound guided ISB or other supraclavicular brachial plexus block) • General anaesthesia with nerve block (not ISB or other supraclavicular brachial plexus block) • General anaesthesia with nerve block (not ISB or other supraclavicular brachial plexus block) and local infiltration analgesia (LIA) • Regional anaesthesia (ultrasound guided ISB or other supraclavicular brachial plexus block)
Comparison	Comparison of the interventions
Outcomes	**Critical**

	• Mortality: within 90 days (dichotomous)
	• Quality of life within 30 days (continuous)
	• Postoperative pain within 30 days (continuous)
	• Hospital readmission within 30 days (dichotomous)
	• Adverse events:
	  ○ Thromboembolic complications within 90 days (VTE; dichotomous)
	  ○ Postoperative neurocognitive decline within 30 days (dichotomous)
	  ○ Phrenic nerve injury within 90 days (dichotomous)
	  ○ Brachial plexus injury within 90 days (dichotomous)
	Important
	• Postoperative use of analgesia (dichotomous)
	• Length of stay (continuous)
	• Nausea within 30 days (dichotomous)
	• Mobilisation within 24 hours after surgery

Study design	Randomised controlled trials If no well-conducted RCTs are available, then observational studies with multivariate analysis will be investigated. Multivariate analysis must account for ASA score and age.

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for trials comparing the effectiveness of intraoperative anaesthesia and analgesia routines utilised for primary shoulder joint replacement surgery.

Five studies were included in the review;[10, 18, 61, 66, 81] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3, Table 4 and Table 5).

1.4.2 Excluded studies

See the excluded studies list in Appendix I:

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
General anaesthesia with LIA versus general anaesthesia with regional anaesthesia				
Bjornholdt 2015[10]	RCT All people received general (total intravenous) anaesthesia. One group had LIA was using ropivacaine and epinephrine. The other group had an interscalene brachial plexus block with ropivacaine given just before surgery.	Adults scheduled for primary shoulder replacement N=69 Mean (SD) age: 65 (8) and 66 (8) ASA: I-III Shoulder replacement: Anatomical total arthroplasty	• Thromboembolic complications • Suspected phrenic nerve palsy • Postoperative use of analgesia • Length of stay	Denmark
Namdari 2017[61]	RCT All people received general anaesthesia. One group had intraoperative LIA with bupivacaine liposome in Exparel suspension. The other group had a preoperative ultrasound guided interscalene brachial plexus blockade using ropivacaine.	People with osteoarthritis or rotator cuff tear arthroplasty scheduled for shoulder replacement N=156 Mean (SD) age: 71 (9) and 68 (8) ASA: Not stated Shoulder replacement: Anatomical or reverse total arthroplasty	• Postoperative pain • Postoperative use of analgesia • Length of stay	USA The study did not state general anaesthesia was utilised however a committee clinical expert stated that general anaesthesia was the only possible anaesthesia given the other analgesic treatments.
Okoroha 2016[66]	RCT All people had general anaesthesia. One group had LIA using lipsomal bupivacaine in Exparel suspension. The other group had a single dose interscalene nerve block 1 hour before surgery using ropivacaine.	Adults undergoing primary shoulder replacement surgery. N=57 Mean (range) age: 67 (49-86) and 69 (50-74) ASA: not stated Shoulder replacement:	• Postoperative pain • Phrenic nerve palsy requiring readmission • Postoperative use of analgesia • Length of stay	USA The study did not state general anaesthesia was utilised however a committee clinical expert stated that general anaesthesia was the only possible anaesthesia given the other analgesic treatments.

Study	Intervention and comparison	Population	Outcomes	Comments
		Anatomical or reverse total arthroplasty		
Regional anaesthesia versus general anaesthesia with or without regional blockade				
Ding 2017[18]	Observational data using New York Statewide Planning and Research Cooperative System (SPARCS) database to compare outcomes from people having regional anaesthesia to those having general anaesthesia with or without regional blockade	People who had total shoulder arthroplasty. N=4158 were retrospectively propensity-matched using nearest-neighbour matching and including a total of 26 covariates. This led to using the data from N=1824 Mean (SD) age: 68 (10) ASA: Not stated Shoulder replacement: Anatomical or reverse total arthroplasty	• Readmission within 90 days • Gastrointestinal complications • Thromboembolic complications • Length of stay	USA
General anaesthesia with peripheral nerve block versus general anaesthesia				
Stundner 2014[81]	Observational data from the Premier database. An administrative database containing discharge information from about 400 acute-care hospitals. All people had general anaesthesia. One group also with an upper-extremity nerve block.	People who had a total shoulder arthroplasty. N=17157 Mean (95% CI) age: 69 (68-69) and 69 (69-69) ASA: not stated Shoulder replacement: unclear if reverse total arthroplasty included	• Readmission • Pulmonary complications • Length of stay	USA All analysis adjusted for age group, gender, ethnicity, Deyo index and presence of sleep apnoea and obesity.

See Appendix D: for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: RCT evidence summary: General anaesthesia with LIA versus general anaesthesia with regional anaesthesia

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with General anaesthesia with regional anaesthesia	Risk difference with General anaesthesia with LIA (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain Mean VAS. Scale from: 0 to 10.	213 (2 studies)	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision		The mean postoperative pain in the control groups was 2.7	The mean postoperative pain in the intervention groups was 1.35 higher (0.37 to 2.32 higher)
Hospital readmission	Not reported				
Thromboembolic complications Pulmonary embolism	65 (1 study)	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	OR 0.13 (0 to 6.61)	31 per 1000	27 fewer per 1000 (from 31 fewer to 145 more)
Postoperative neurocognitive decline	Not reported				
Phrenic nerve palsy Suspected or requiring readmission	122 (2 studies)	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	OR 0.14 (0.01 to 2.32)	32 per 1000	27 fewer per 1000 (from 31 fewer to 39 more)
Brachial plexus injury	Not reported				
Postoperative use of analgesia Narcotic consumption	213 (2 studies)	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision		The mean postoperative use of analgesia in the control groups was 17 morphine equivalent units	The mean postoperative use of analgesia in the intervention groups was 3.33 lower (9.04 lower to 2.74 higher)
Postoperative use of analgesia[4]	65 (1 study)	Deemed to be at very high risk of bias.	Median (IQR) in mg General anaesthesia with LIA: 95 (170-150)		Not estimable

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with General anaesthesia with regional anaesthesia	Risk difference with General anaesthesia with LIA (95% CI)
Median opioid consumption		Imprecision unclear.	General anaesthesia with non-ISB nerve block: 40 (8-76)		
Length of stay	213 (2 studies)	⨁⨁⨁⊖ MODERATE[1,3] due to risk of bias		The mean length of stay in the control groups was 1.65 days	The mean length of stay in the intervention groups was 0.17 lower (0.37 lower to 0.03 higher)
Median length of stay[4]	65 (1 study)	Deemed to be at very high risk of bias. Imprecision unclear.	Median (range) in days General anaesthesia with LIA: 2 (1-6) General anaesthesia with non-ISB nerve block: 2 (1-3)		Not estimable

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Outcome reported as a median and it was not possible to assess the precision or to calculate the absolute effect and therefore grade the overall quality..

Table 4: Non-randomised evidence summary: Regional anaesthesia versus general anaesthesia with or without regional blockade

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with General anaesthesia with or without regional blockade	Risk difference with Regional anaesthesia (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain	Not reported				
Readmission	1824 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.64 (0.43 to 0.96)	65 per 1000	23 fewer per 1000 (from 3 fewer to 37 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with General anaesthesia with or without regional blockade	Risk difference with Regional anaesthesia (95% CI)
Thromboembolic complications DVT or PE	1824 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 2 (0.18 to 22.02)	1 per 1000	1 more per 1000 (from 1 fewer to 23 more)
Postoperative neurocognitive decline	Not reported				
Phrenic nerve injury	Not reported				
Brachial plexus injury	Not reported				
Length of stay	1824 (1 study)	⨁⊖⊖⊖ VERY LOW[1] due to risk of bias		The mean length of stay in the control groups was 2 days	The mean length of stay in the intervention groups was 0.3 higher (0.2 to 0.4 higher)
Nausea gastrointestinal complications	1824 (1 study)	⨁⊖⊖⊖ VERY LOW[1] due to risk of bias	RD 0 (0 to 0)	0 per 1000	0 fewer per 1000 (from 0 more to 0 more)[3]

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effect calculated using the risk difference.

Table 5: Non-randomised evidence summary: General anaesthesia with peripheral nerve block versus general anaesthesia

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with General anaesthesia	Risk difference with General anaesthesia with peripheral nerve block (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain	Not reported				

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with General anaesthesia	Risk difference with General anaesthesia with peripheral nerve block (95% CI)
Intensive care unit admission	17157 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	OR 1.16 (0.93 to 1.45)	Not estimable	Not estimable
Pulmonary complications pulmonary embolism, pneumonia, and pulmonary compromise	17157 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	OR 0.87 (0.66 to 1.15)	Not estimable	Not estimable
Postoperative neurocognitive decline	Not reported				
Phrenic nerve injury	Not reported				
Brachial plexus injury	Not reported				
Increased length of stay	17157 (1 study)	⨁⊖⊖⊖ VERY LOW[1] due to risk of bias	OR 0.89 (0.82 to 0.97)	Not estimable	Not estimable

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

See Appendix F: for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified in the literature search, however, one original threshold analysis was conducted which can be found in Appendix I: Nerve block threshold analysis

1.5.2 Excluded studies

One health economic study [33] was excluded due to assessment of methodological limitations.

See also the health economic study selection flow chart in Appendix G:

1.5.3 Summary of studies included in the economic evidence review

No studies were included

1.5.4 Health economic modelling

A threshold analysis was conducted on the addition of nerve blocks to an anaesthetic regimen. This was conducted as the committee agreed that nerve blocks are likely to be a costly intervention. LIA, on the other hand, is a much cheaper intervention. No economic evidence was found for either intervention.

The method and results of the analysis can be found in Appendix I: Nerve block threshold analysis. The analysis uses estimates of incremental cost to find what QALY or utility gain is required at a given threshold of cost effectiveness. The threshold selected for this analysis was £20,000 in line with the NICE reference case. A range of incremental costs driven by the time required to administer the nerve block (30 minutes, 10 minutes and 5 minutes) and if the cost of theatre time was incorporated (yes or no) were included in the analysis. The rationale for having theatre time included as a cost variable is that the committee suggested that if 2 anaesthetists are available a nerve block can be administered in the anaesthesia room, not incurring additional theatre time costs. Therefore, for scenarios where theatre time was not included, 2 consultant anaesthetists were costed in. Whereas when theatre time was included, only one consultant anaesthetist was costed in. The results found that a nerve block is unlikely to be cost effective the longer it takes to administer, the shorter the effect duration, and if theatre time cost is included. However there are circumstances, such as when administration time is short, effect duration is long and theatre time is not included, when a nerve block could be cost effective. The different combinations of these factors are present across the NHS, so nerve blocks may be a viable cost-effective anaesthetic intervention for some hospitals but not for others.

1.5.5 Unit costs

Relevant unit costs for the addition of a nerve block to an anaesthetic regimen are provided

Table **6** to aid consideration of cost effectiveness. A cost utility analysis from 2015 that looked at the cost effectiveness of anaesthetic regimens in a hip and knee replacement population [57] stated that an injection of LIA costed £2.00 per unit**.**

Table 6: UK 2018 cost for the addition of a nerve block to an anaesthetic regimen for primary elective joint replacement when varying administration time and the inclusion of theatre time cost

Extra time in theatre	Resource	Unit cost	Source
5 min	Biogel	£1.07	NHS Hospital
	Chlorhexidine	£1.08	NHS Hospital
	Vial with Lidocaine 1% 10ml ampoule	£0.38	BNF
	Vial of 0.5% Levobupivacaine (5mg/ml)	£3.88	BNF
	Syringes (10ml)	£0.06	NHS Hospital
	Filter needle	£0.23	NHS Hospital
	Regional block needle	£5.78	NHS Hospital
	Hypodermic needle	£1.35	NHS Hospital
	Cost per consultant anaesthetist (£1.80 per minute)	£9.00	PSSRU 2018

	Total cost excluding theatre time[(a)]	**£31.83**	
	Cost of theatre time (£20.50 per min)	£102.50	CG124
	Total cost including theatre time[(b)]	**£125.33**	
10 min	Biogel	£1.07	NHS Hospital
	Chlorhexidine	£1.08	NHS Hospital
	Vial with Lidocaine 1% 10ml ampoule	£0.38	BNF
	Vial of 0.5% Levobupivacaine (5mg/ml)	£3.88	BNF
	Syringes (10ml)	£0.06	NHS Hospital
	Filter needle	£0.23	NHS Hospital
	Regional block needle	£5.78	NHS Hospital
	Hypodermic needle	£1.35	NHS Hospital
	Cost per consultant anaesthetist (£1.80 per minute)	£18.00	PSSRU 2018
	Total cost excluding theatre time[(a)]	**£49.83**	
	Cost of theatre time (£20.50 per min)	£205.00	CG124
	Total cost including theatre time[(b)]	**£236.83**	NHS Hospital
30 min	Biogel	£1.07	NHS Hospital
	Chlorhexidine	£1.08	NHS Hospital
	Vial with Lidocaine 1% 10ml ampoule	£0.38	BNF
	Vial of 0.5% Levobupivacaine (5mg/ml)	£3.88	BNF
	Syringes (10ml)	£0.06	NHS Hospital
	Filter needle	£0.23	NHS Hospital
	Regional block needle	£5.78	NHS Hospital
	Hypodermic needle	£1.35	NHS Hospital
	Cost per consultant anaesthetist (£1.80 per minute)	£54.00	PSSRU 2018
	Total cost excluding theatre time[(a)]	**£121.83**	
	Cost of theatre time (£20.50 per min)	£615.00	CG124
	Total cost including theatre time[(b)]	**£682.83**	NHS Hospital

Source: PSSRU (Personal Social Services Research Unit)[15]; CG124[64]

(a) Total costs excluding theatre time included the cost of 2 anaesthetists

(b) It was assumed that the cost of theatre time from CG124[64] did not include personnel costs

(c) NHS Hospital is Peterborough and Stamford Hospitals NHS Foundation Trust which provided information for CG124[64]

1.6 Evidence statements

1.6.1 Clinical evidence statements

3 RCTs (n=282) comparing general anaesthesia with LIA to general anaesthesia with regional anaesthesia found a benefit for general anaesthesia with regional anaesthesia in postoperative pain and postoperative use of analgesia. General anaesthesia with LIA was better in phrenic nerve palsy. There was no difference between interventions in thromboembolic complications and 2 length of stay outcomes. Nearly all outcomes were deemed to be of very low quality though 1 length of stay outcome was moderate quality.

1 non-randomised study (n=4158) reported on regional anaesthesia versus general anaesthesia with or without regional blockade. This was a retrospectively propensity-matched sample of 1824 people and it found a benefit for regional anaesthesia in readmission. There was a benefit for general anaesthesia with or without regional blockade in thromboembolic complications. No difference was seen between interventions in length of stay or gastrointestinal complications. All outcomes were graded very low quality.

1 non-randomised study (n=17,157) reported on General anaesthesia with peripheral nerve block versus general anaesthesia. This was a sample of 17157 people with multivariate analysis. All outcomes indicated no difference between interventions; these were intensive care unit admission, pulmonary complications, and length of stay. All outcomes were graded very low quality.

1.6.2 Health economic evidence statements

One original threshold analysis for the addition of a nerve block to any anaesthetic regimen found that nerve blocks are unlikely to be cost effective if theatre time is included in the incremental cost or if administration time is longer. However, it is possible the addition of a nerve block is cost effective if administration time is short, the cost of theatre time is not included and if the duration of effect used in the analysis is longer. The cost of theatre time can be excluded when there are two anaesthetists present so that the nerve block can be administered in the anaesthesia room, therefore not taking up extra theatre time.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The critical outcomes are mortality, quality of life, postoperative pain, postoperative neurocognitive decline, thromboembolic complications, hospital readmission, phrenic nerve injury, and brachial plexus injury. The time point for mortality, the most critical outcome, was specified to within 90 days because the committee were concerned that there are confounding factors that will not be adequately resolved over longer time periods. There are many factors outside of anaesthetic used during joint replacement surgery that contribute towards mortality and these expand as a person moves further on in their life. The committee were aware the trials would not be of an adequate size to equalise these factors between treatment groups. Postoperative pain is of critical importance as it represents a central aspect of a person's initial experience of the joint replacement surgery. In addition the committee agreed that there is an argument that acute pain is a predictor of chronic pain and therefore reducing postoperative pain may future chronic pain. There are adverse events that are key decision making outcomes for the people undergoing joint replacement surgery. These are thromboembolic complications, neurocognitive decline, phrenic nerve injury, and brachial plexus injury.

Important outcomes are postoperative use of analgesia, length of stay, nausea, and mobilisation within 24 hours after surgery. Postoperative use of analgesia is an indirect indicator of postoperative pain and as such is a useful measure for anaesthetic approach. Reduced length of stay is very important to those undergoing surgery and has economic implications. The anaesthetic approach may impact on when a person can mobilise after surgery. A person's ability mobilise shortly after surgery represents the early experience of joint replacement and also whether they can be discharged from hospital.

1.7.1.2 The quality of the evidence

In outcomes where it was possible to assess using GRADE methodology, all but 1 were deemed to be of very low quality. The 2 outcomes not graded were assessed to be at very high risk of bias. The outcomes from the 3 randomised controlled trials were at risk of bias often due to unclear allocation concealment and also due to lack of blinding for subjective outcomes. 2 RCTs did not state that general anaesthesia was used in the studies though this was stated to be the only possibility by a committee member. Both study outcomes were judged to be a higher risk of bias due to this omission. The non-randomised study outcomes were commonly downgraded due to lack of comparability of care between groups. Most outcomes across the evidence review were also downgraded for imprecision.

1.7.1.3 Benefits and harms

5 studies covering 3 comparisons were found for this evidence review. 3 randomised controlled trials evaluated general anaesthesia with LIA versus general anaesthesia with regional analgesia. A non-randomised study investigated regional anaesthesia versus general anaesthesia with or without regional blockade and a further non-randomised study looked at general anaesthesia with peripheral nerve block versus general anaesthesia.

General anaesthesia with LIA versus general anaesthesia with regional analgesia found a benefit for general anaesthesia with LIA in thromboembolic complications and phrenic nerve palsy. There was a benefit for general anaesthesia with regional analgesia in postoperative pain and median postoperative use of analgesia. No difference was seen in a further postoperative use of analgesia outcome and for 2 length of stay outcomes. The committee discussed the two outcomes favouring general anaesthesia with LIA, both were adverse events and involved low numbers of events. The thromboembolic complication outcome was 1 pulmonary embolism that occurred and thromboembolic complications are not overtly associated with regional anaesthesia. Therefore the committee concluded that this could well have been an event that happened by chance and may not have been associated with the anaesthesia treatment. However phrenic nerve palsy is a direct procedural complication associated with interscalene brachial plexus block (ISB) (regional anaesthesia) and there were 2 events across the 2 studies. The committee agreed to that it was reasonable to say these results are not simply down to chance and are a negative effect of regional anaesthesia that should be considered. The phrenic nerve is often blocked as a side effect of interscalene brachial plexus block, but the impact of this is likely to last less than 24 hours. Neuropraxia and permanent damage to the phrenic nerve are rare but can cause long-term effects on respiratory function.

The committee spoke about the mean pain outcome taken from 2 RCTs. Both studies indicated a benefit for general anaesthesia with regional analgesia in pain 8 hours after surgery. However both studies also indicated a reversal in this by 24 hours after surgery when general anaesthesia with LIA had less pain. 24 hours after surgery the analgesic effects of the general anaesthesia and the nerve blocks and the LIA would not be present. The committee conjectured that both forms of anaesthesia having worn off after 24 hours then the groups must have had differing analgesic routines. These may well have not been planned or stated differences but it could have been that due to the people in the LIA group having more pain in the early hours of recovery, they are topped up with analgesia more

readily than those in the regional analgesia group. This increased pain may have led to the clinically insignificant increased length of stay in the regional analgesia group.

The regional anaesthesia versus general anaesthesia with or without regional blockade comparison was taken from observational data in a propensity score matched group of 1824 people. A benefit of regional anaesthesia was found for readmission and a benefit of general anaesthesia with or without regional blockade in terms of thromboembolic complications. The benefit in terms of readmission made sense to the committee because respiratory complications from general anaesthesia could drive readmission. No difference was found in length of stay or gastrointestinal complications. The use of regional anaesthesia when not combined with general anaesthesia was considered by the committee to be a possible predictor of the future of anaesthesia in shoulder replacement surgery. The movement towards day surgery for shoulder replacement means that anaesthetic strategies that allow for swifter discharge are of increased prominence. Regional anaesthesia when not combined with general anaesthesia can regularly lead to discharge on the same day supporting day surgery.

The final comparison was general anaesthesia with peripheral nerve block versus general anaesthesia in an observational cohort of over 17 thousand operations. Multivariate analysis was used to address issues of confounding. There was no difference between treatment arms for intensive care unit admission, pulmonary complications, or length of stay.

The committee spoke more generally about the practicalities of regional anaesthesia, ISBs can take anywhere from 5 minutes to 45 minutes to complete. The expectation of how long the block might take affects how surgery lists are put together and if it takes a long time to complete the block then surgeries might be delayed for a day and increasing the backlog. The committee agreed that this is dependent on how many anaesthetists are working in the operating room and how the surgery anaesthesia is organised.

Overall the committee did not feel the evidence or committee consensus supported recommending any specific anaesthetic approach. The benefits of general anaesthesia with LIA and regional anaesthesia with LIA were potentially offset by adverse events. However the committee recognised the importance of discussing different anaesthesia options with people having shoulder replacement surgery and recommended this.

In addition the committee did not feel the evidence as it currently stands adequately explores anaesthesia for shoulder joint replacement and made 2 research recommendations. Firstly the committee felt that the 3 RCTs investigating general anaesthesia with LIA versus general anaesthesia with regional analgesia were small and the outcomes were graded as very low quality. Therefore the committee has made a research recommendation to cover this important comparison with the additional important comparator, general with nerve block. Secondly the committee understands that regional anaesthesia alone allows for faster discharge and could allow for day case shoulder joint replacement. This may be the future of shoulder joint replacement and there is currently very little evidence using this intervention. The move towards this might allow for more day cases and research into this intervention could be prominent for the future shoulder replacement anaesthesia.

1.7.2 Cost effectiveness and resource use

No economic evidence was found for this population and as such, there was uncertainty about the cost effectiveness of the interventions. Unit costs for LIA and the addition of nerve block to an anaesthetic regimen were presented. The committee acknowledged that the presented unit costs for the addition of nerve blocks did not factor in any cost savings, However they were clearly a more expensive intervention than LIA.

Given the lack of evidence and uncertainty surrounding the augmentation of an anaesthetic regimen with nerve blocks, a threshold analysis was conducted. The analysis showed what gain in quality adjusted life years (QALY) and health related quality of life (HRQoL) is

necessary for an anaesthetic regimen augmented with nerve block to be cost effective at a threshold of £20,000 per QALY. Three factors highlighted by the committee as variable across the NHS were explored in the analysis. These factors were the time it takes to administer the nerve block (5 minutes, 10 minutes and 30 minutes); the length of time that the nerve block has an effect for (24 hours, 3 days, 10 days and 30 days); and if the cost of theatre time should be included or not. The rationale for having theatre time included as a cost variable was that the committee suggested that if 2 anaesthetists are available a nerve block can be administered in the anaesthesia room, not incurring additional theatre time costs. Therefore, for scenarios where theatre time was not included, 2 consultant anaesthetists were costed in. Whereas when theatre time was included, only one consultant anaesthetist was costed in.

Outlined below is the QALY gain needed based on the time taken to administer the nerve block and whether or not theatre time was included:

- Administration time 30 minutes with theatre time: 0.034
- Administration time 10 minutes with theatre time: 0.012
- Administration time 5 minutes with theatre time: 0.006
- Administration time 30 minutes with no theatre time: 0.006
- Administration time 10 minutes with no theatre time: 0.002
- Administration time 5 minutes with no theatre time: 0.002

The gain in HRQoL necessary at range of time horizons for all scenarios listed in the bullet points above was calculated (24 hours, 3 days, 10 days and 30 days). The results indicated that for a number of scenarios; particularly when the time to administer was 30 minutes, the intervention effect was 24 hours and when the cost of theatre time was included; the likelihood of nerve blocks being cost effective was impossible given that the gain in HRQoL needed was greater than 1 (given the assumed scale ranges from 0 to 1). When the assumptions were softened to their respective middle values, the gain in HRQoL was often not impossible (the gain needed was less than 1) but improbable. Finally, when time to administer was 5 minutes, the intervention effect was 30 days and when theatre time was excluded, the gain in HRQoL and therefore cost-effectiveness was more realistic.

The committee acknowledged that the time required for administration and the inclusion of the cost of theatre time was dependent on the experience of the anaesthetist and if two anaesthetists are available, respectively. All combinations of personnel numbers and time taken for administration can be found on the NHS at present. The length of time that nerve blocks have an effect could be argued to be anything between a matter of hours to a lifetime. The analgesic effect of a nerve block is variable but may be up to 18 hours on average for shoulder replacements. However, a 24 hour time horizon may be the most appropriate when considering acute post-operative outcomes (for example, pain, post-operative nausea and vomiting). A longer effect duration of 10 days to 30 days may be most appropriate to account for the possible effect of anaesthetic choice on adverse clinical outcomes (for example post-operative morbidity and mortality). Lastly, an even longer time horizon would be needed to account for long term outcomes (such as chronic pain, opioid dependence and range of motion).

There was discussion as to whether the addition of nerve blocks requires additional theatre time, and therefore the associated costs, specific to the procedure. This was dependent on the presence of a second anaesthetist. If 2 anaesthetists are present during surgery a nerve block can be administered in the anaesthesia room, therefore not incurring additional theatre time. This would represent additional staff costs.

A nerve block may take up to 5 minutes to administer for those who are familiar with the procedure. There may be further additional time required initially for those who are not familiar with using nerve blocks. Some members of the committee shared experience of

nerve block administration time being as high as 45 minutes, although this would be a rarity. The efficacy of nerve blocks is also dependent how experienced the anaesthetist is. As a result analgesics are often used pre-emptively which allows the majority of people to leave at 24 hours. Analgesics are relatively low cost drugs.

In comparison, LIA can be administered by the surgeon and is likely to take around 5 minutes. This would represent a neutral cost, in terms of theatre time, if the nerve block performed by the anaesthetist takes an equivalent time and is performed during usable theatre time (for example, it is not performed before the list start time or during the previous operation by a second anaesthetist or a “block team"). More hospitals are developing block teams who administer the blocks in the anaesthetic rooms or elsewhere during the previous operations, thereby not impacting on usable theatre time. If the nerve block is performed during usable theatre time but takes consistently longer than the time taken for the surgeon to administer LIA, LIA could be cost saving as a result of reduced theatre time.

In addition to the uncertainty regarding costs, the committee also thought there was uncertainty in the clinical evidence for the shoulder replacement population. Given this the committee were unable to recommend specific options. A consensus recommendation was made to discuss all of the options with people having primary elective shoulder replacement. This recommendation is not expected to have a significant resource impact as it will not change current practice

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Appendices

Appendix A: Review protocols

Table 7: Review protocol: Anaesthesia for elective shoulder joint replacement

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Anaesthesia in shoulder joint replacement surgery
2.	Review question	In adults having primary elective shoulder joint replacement, what is the most clinical and cost effective intraoperative anaesthetic approach?
3.	Objective	This review seeks to assess the most effective analgesia for total joint replacement. These can include regional or general anaesthetic alone or in combination with each other, nerve blocks or local infiltration.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Epistemonikos Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain	Primary elective shoulder joint replacement surgery

ID	Field	Content
	being studied	
6.	Population	Inclusion: Adults having primary elective shoulder joint replacement Exclude studies including people meeting any of the following criteria: Adults having joint replacement as immediate treatment following fracture. Adults having revision joint replacement. Adults having joint replacement as treatment for primary or secondary cancer affecting the bones.
7.	Intervention/Exposure/Test	General anaesthesia General anaesthesia with local infiltration analgesia (LIA) General anaesthesia with regional anaesthesia (ultrasound guided ISB or other supraclavicular brachial plexus block) General anaesthesia with nerve block (not ISB or other supraclavicular brachial plexus block) General anaesthesia with nerve block (not ISB or other supraclavicular brachial plexus block) and local infiltration analgesia (LIA) Regional anaesthesia (ultrasound guided ISB or other supraclavicular brachial plexus block)
8.	Comparator/Reference standard/Confounding factors	Comparison of interventions.
9.	Types of study to be included	Systematic reviews RCTs If no well-conducted RCTs are available, then observational studies with multivariate analysis will be investigated.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	Mortality: upto 90 days (dichotomous) Quality of life up to 30 days (continuous) Postoperative pain up to 30 days (continuous) Postoperative neurocognitive decline up to 30 days (dichotomous) Thromboembolic complications up to 90 days (VTE; dichotomous)

ID	Field	Content
		Hospital readmission up to 30 days (dichotomous) Adverse events: Phrenic nerve injury within 90 days (dichotomous) brachial plexus injury within 90 days (dichotomous)
13.	Secondary outcomes (important outcomes)	Postoperative use of analgesia (dichotomous) Length of stay (continuous) Nausea up to 30 days (dichotomous) Mobilisation (ambulation) within 24 hours after surgery
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95%

ID	Field	Content	
		confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. If the population included in an individual study includes children aged under 12, it will be included if the majority of the population is aged over 12, and downgraded for indirectness if the overlap into those aged less than 12 is greater than 20%. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.	
17.	Analysis of sub-groups	Age: <60 years old, ≥60 years old Co-morbidities: I-II ASA Grade, III-IV ASA Grade Form of shoulder replacement: Shoulder hemiarthroplasty, total shoulder replacement (anatomical), total shoulder replacement (reverse anatomy)	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)

ID	Field	Content		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	05/04/19		
22.	Anticipated completion date	20/03/20		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☐
		Piloting of the study selection process	☑	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Headches@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Alex Allen [Senior Systematic Reviewer] Rafina Yarde [Systematic reviewer] Robert King [Health economist] Agnes Cuyas [Information specialist]		

ID	Field	Content	
		Eleanor Priestnall [Project Manager]	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Knee joint replacement surgery, arthroplasty, anaesthesia, analgesia	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued

ID	Field	Content
35.	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Table 8: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from low or middle-income countries (e.g. most non-OECD countries) or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[63] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example,

	Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[63]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 01 May 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 01 May 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 5 of 12 CENTRAL to 2019 Issue 5 of 12	None
Epistemonikos	Inception – 01 May 2019	None

Medline (Ovid) search terms

1.	arthroplasty/ or arthroplasty, replacement/ or arthroplasty, replacement, hip/ or arthroplasty, replacement, knee/ or arthroplasty, replacement, shoulder/ or hemiarthroplasty/
2.	joint prosthesis/ or hip prosthesis/ or knee prosthesis/ or shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.

15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	exp Anesthesia/
26.	((an?esthet* or an?esthesia) adj4 (regional* or local* or general or spinal or epidural)).ti,ab.
27.	Nerve Block/
28.	((nerve* or neurax* or regional or peripheral*) adj3 block*).ti,ab.
29.	((plexus or sciatic* or interscalene or femor* or tibia* or posterior or obturator or fascia iliaca) adj3 block).ti,ab.
30.	(CNB or PNB or FNB or TNB or ONB or LPB or ISBB or FIB or LIA).ti,ab.
31.	((periarticular or local*) adj2 infiltration).ti,ab.
32.	or/25-31
33.	24 and 32
34.	randomized controlled trial.pt.
35.	controlled clinical trial.pt.
36.	randomi#ed.ti,ab.
37.	placebo.ab.
38.	randomly.ti,ab.
39.	Clinical Trials as topic.sh.
40.	trial.ti.
41.	or/34-40
42.	Meta-Analysis/
43.	exp Meta-Analysis as Topic/
44.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
45.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
46.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
47.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
48.	(search* adj4 literature).ab.
49.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
50.	cochrane.jw.
51.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
52.	or/42-51
53.	Epidemiologic studies/
54.	Observational study/
55.	exp Cohort studies/
56.	(cohort adj (study or studies or analys* or data)).ti,ab.

57.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
58.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
59.	Controlled Before-After Studies/
60.	Historically Controlled Study/
61.	Interrupted Time Series Analysis/
62.	(before adj2 after adj2 (study or studies or data)).ti,ab.
63.	or/54-63
64.	exp case control study/
65.	case control*.ti,ab.
66.	or/65-66
67.	64 or 67
68.	Cross-sectional studies/
69.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
70.	or/69-70
71.	64 or 71
72.	64 or 67 or 71
73.	33 and (41 or 52 or 72)

Embase (Ovid) search terms

1.	*arthroplasty/ or *replacement arthroplasty/ or *hip replacement/ or *knee replacement/ or *shoulder replacement/ or *hemiarthroplasty/
2.	*joint prosthesis/ or *hip prosthesis/ or *knee prosthesis/ or *shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	*anesthesia/ or general anesthesia/ or regional anesthesia/
24.	((an?esthet* or an?esthesia) adj4 (regional* or local* or general or spinal or

	epidural)).ti,ab.
25.	nerve block/
26.	((nerve* or neurax* or regional or peripheral*) adj3 block*).ti,ab.
27.	((plexus or sciatic* or interscalene or femor* or tibia* or posterior or obturator or fascia iliaca) adj3 block).ti,ab.
28.	(CNB or PNB or FNB or TNB or ONB or LPB or ISBB or FIB or LIA).ti,ab.
29.	((periarticular or local*) adj2 infiltration).ti,ab.
30.	or/23-29
31.	22 and 30
32.	random*.ti,ab.
33.	factorial*.ti,ab.
34.	(crossover* or cross over*).ti,ab.
35.	((doubl* or singl*) adj blind*).ti,ab.
36.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
37.	crossover procedure/
38.	single blind procedure/
39.	randomized controlled trial/
40.	double blind procedure/
41.	or/32-40
42.	systematic review/
43.	meta-analysis/
44.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
45.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
46.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
47.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
48.	(search* adj4 literature).ab.
49.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
50.	cochrane.jw.
51.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
52.	or/42-51
53.	Clinical study/
54.	Observational study/
55.	family study/
56.	longitudinal study/
57.	retrospective study/
58.	prospective study/
59.	cohort analysis/
60.	follow-up/
61.	cohort*.ti,ab.
62.	61 and 62
63.	(cohort adj (study or studies or analys* or data)).ti,ab.
64.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
65.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or

	review or analys* or cohort* or data)).ti,ab.
66.	(before adj2 after adj2 (study or studies or data)).ti,ab.
67.	or/54-60,63-67
68.	exp case control study/
69.	case control*.ti,ab.
70.	or/69-70
71.	68 or 71
72.	cross-sectional study/
73.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
74.	or/73-74
75.	68 or 75
76.	68 or 71 or 75
77.	31 and (41 or 52 or 76)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Arthroplasty] this term only
#2.	MeSH descriptor: [Arthroplasty, Replacement] this term only
#3.	MeSH descriptor: [Arthroplasty, Replacement, Hip] this term only
#4.	MeSH descriptor: [Arthroplasty, Replacement, Knee] this term only
#5.	MeSH descriptor: [Arthroplasty, Replacement, Shoulder] this term only
#6.	MeSH descriptor: [Hemiarthroplasty] this term only
#7.	(or #1-#6)
#8.	MeSH descriptor: [Joint Prosthesis] this term only
#9.	MeSH descriptor: [Hip Prosthesis] this term only
#10.	MeSH descriptor: [Knee Prosthesis] this term only
#11.	MeSH descriptor: [Shoulder Prosthesis] this term only
#12.	(or #8-#11)
#13.	((joint* or knee* or shoulder* or hip*) near/5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)):ti,ab
#14.	(or #7, #12-#13)
#15.	MeSH descriptor: [Anesthesia] explode all trees
#16.	((anaesthet* or anesthet* or anaesthesia or anesthesia) near/4 (regional* or local* or general or spinal or epidural)):ti,ab
#17.	MeSH descriptor: [Nerve Block] this term only
#18.	((nerve* or neurax* or regional or peripheral*) near/3 block*):ti,ab
#19.	((plexus or sciatic* or interscalene or femor* or tibia* or posterior or obturator or fascia iliaca) near/3 block):ti,ab
#20.	(CNB or PNB or FNB or TNB or ONB or LPB or ISBB or FIB or LIA):ti,ab
#21.	((periarticular or local*) near/2 infiltration):ti,ab
#22.	(or #15-#21)
#23.	#14 and #22

Epistemonikos search terms

1.	((joint* OR knee* OR shoulder* OR hip*) AND (surger* OR replace* OR prosthe* OR endoprosthe* OR implant* OR artificial OR arthroplast* OR hemiarthroplast*)) AND (((an?esthet* OR an?esthesia) AND (regional* OR local* OR general OR spinal OR epidural)) OR ((nerve* OR neurax* OR regional OR peripheral*) AND block*) OR ((plexus OR sciatic* OR interscalene OR femor* OR tibia* OR posterior OR obturator OR fascia iliaca) AND block) OR (CNB OR PNB OR FNB OR TNB OR ONB OR LPB

	OR ISBB OR FIB OR LIA) OR ((periarticular OR local*) AND infiltration)) [Filters: protocol=no, classification=systematic-review]

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the joint replacement population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run in Medline and Embase.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 01 May 2019	Exclusions Health economics studies
Embase	2014 – 01 May 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 01 May 2019 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	arthroplasty/ or arthroplasty, replacement/ or arthroplasty, replacement, hip/ or arthroplasty, replacement, knee/ or arthroplasty, replacement, shoulder/ or hemiarthroplasty/
2.	joint prosthesis/ or hip prosthesis/ or knee prosthesis/ or shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.

22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	Economics/
26.	Value of life/
27.	exp "Costs and Cost Analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, Medical/
30.	Economics, Nursing/
31.	Economics, Pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp Budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41

Embase (Ovid) search terms

1.	*arthroplasty/ or *replacement arthroplasty/ or *hip replacement/ or *knee replacement/ or *shoulder replacement/ or *hemiarthroplasty/
2.	*joint prosthesis/ or *hip prosthesis/ or *knee prosthesis/ or *shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/

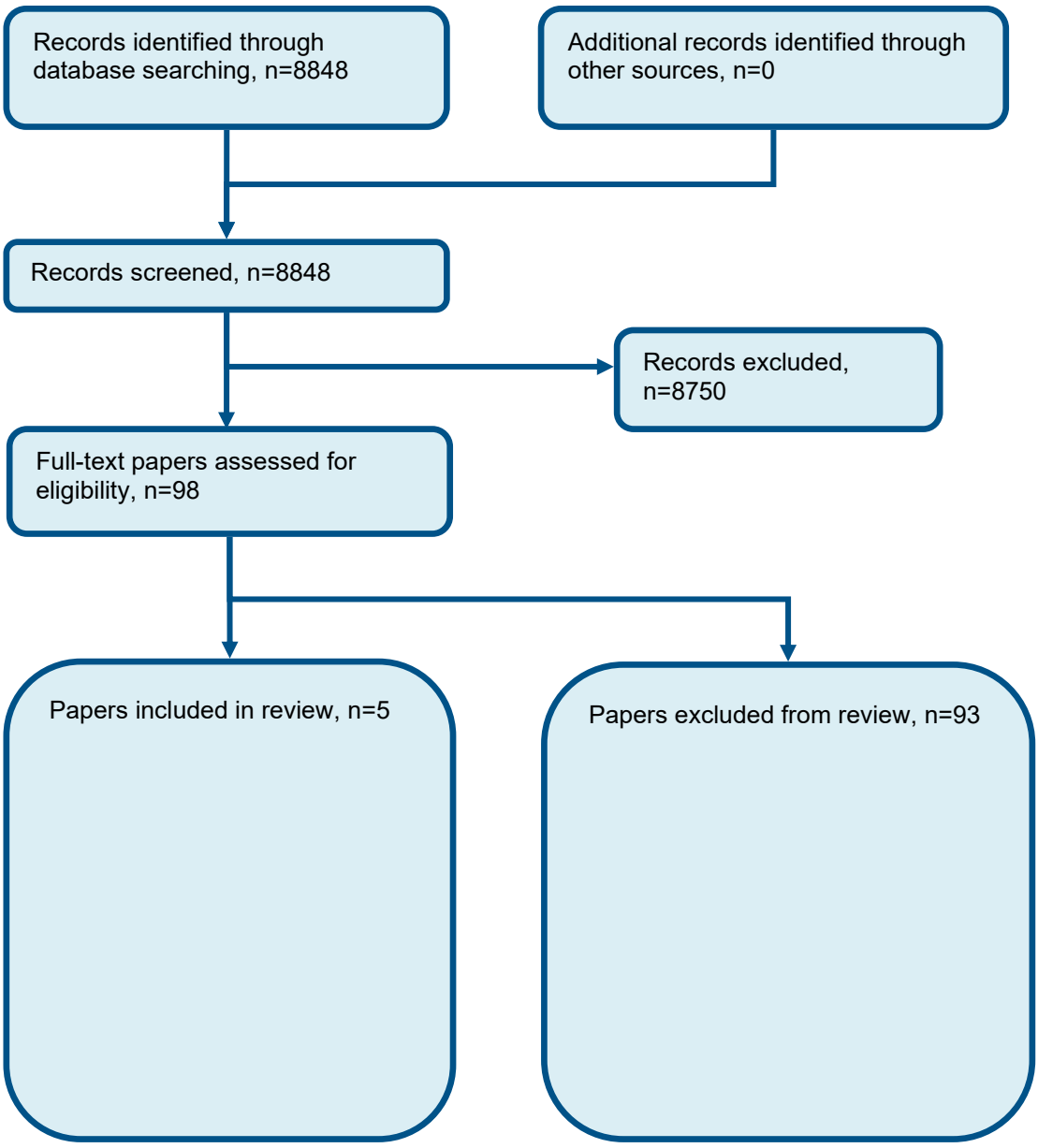
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR arthroplasty
#2.	MeSH DESCRIPTOR arthroplasty, replacement
#3.	MeSH DESCRIPTOR arthroplasty, replacement, hip
#4.	MeSH DESCRIPTOR arthroplasty, replacement, knee
#5.	MeSH DESCRIPTOR arthroplasty, replacement, shoulder
#6.	MeSH DESCRIPTOR hemiarthroplasty
#7.	MeSH DESCRIPTOR joint prosthesis
#8.	MeSH DESCRIPTOR hip prosthesis
#9.	MeSH DESCRIPTOR knee prosthesis
#10.	MeSH DESCRIPTOR shoulder prosthesis
#11.	(((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)))
#12.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) IN NHSEED
#13.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) IN HTA

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of Anaesthesia for elective shoulder joint replacement



Appendix D: Clinical evidence tables

Study	Bjornholdt 2015[10]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=69)
Countries and setting	Conducted in Denmark; Setting: Aarhus University Hospital and Horsens Regional Hospital
Line of therapy	Not applicable[1]
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults scheduled for primary shoulder replacement
Exclusion criteria	Severe chronic neuropathic pain or sensory disturbances in the shoulder, recent shoulder fracture, reverse prosthesis shoulder replacement, operation performed without general anaesthesia, allergy to amid-type local anaesthetics, over 90 years old, pregnant, unable to provide informed consent.
Age, gender and ethnicity	Age - Mean (SD): 65 (8) and 66 (8). Gender (M:F): 34/37. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III). 3. Form of shoulder replacement:: Total shoulder replacement (anatomical)
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: General and regional - General anaesthesia with regional anaesthesia (ultrasound guided ISB or other supraclavicular brachial plexus block). General (total intravenous) anaesthesia. Interscalene brachial plexus block with ropivacaine given just before surgery (with the person in supine position). . Duration Surgery. Concurrent medication/care: Postoperative IV morphine given as required. Rescue interscalene brachial plexus block performed if pain could no be controlled. All people received acetaminophen and ibuprofen. . Indirectness: No indirectness (n=36) Intervention 2: General - General anaesthesia with local infiltration analgesia (LIA). General (total

[1] If an anaesthetic doesn't appear to be working then often the anaesthetist will supplement this with analgesics

Study	Bjornholdt 2015[10]
	intravenous) anaesthesia. The LIA was administered with 3 syringes with ropivacaine (2 also containing epinephrine) around the axillary nerve, glenoid cavity, medial rotator cuff, posterior joint capsule and surrounding tissue, suprascapular notch, tissue around the humerus, anterior part of the joint, subscapular muscle, anterior tissue on the operative site including subcutaneous tissue. . Duration Surgery. Concurrent medication/care: Postoperative IV morphine given as required. Rescue interscalene brachial plexus block performed if pain could no be controlled. All people received acetaminophen and ibuprofen. . Indirectness: No indirectness
Funding	Funding not stated (Author reports grants from The Heath Research Fund of Central Denmark, Augustinus Foundation. The Family Hede Nielsen Foundation, The Danish Rheumatism Association during the study.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (LIA) versus GENERAL ANAESTHESIA WITH REGIONAL ANAESTHESIA (ULTRASOUND GUIDED ISB OR OTHER SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK)

Protocol outcome 1: Thromboembolic complications at within 90 days
- Actual outcome: Pulmonary embolism at 8 days after surgery; Group 1: 0/33, Group 2: 1/32
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 surgical procedure changed, 1 protocol not followed; Group 2 Number missing: 1, Reason: 1 surgical procedure changed,

Protocol outcome 2: Adverse events: phrenic nerve injury at within 90 days of surgery
- Actual outcome: Suspected phrenic nerve palsy at Unclear; Group 1: 0/33, Group 2: 1/32
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 surgical procedure changed, 1 protocol not followed; Group 2 Number missing: 1, Reason: 1 surgical procedure changed,

Protocol outcome 3: Postoperative use of analgesia at as reported
- Actual outcome: Median opioid consumption at Within 24 hours after surgery; Median (IQR): general anaesthesia with LIA: 95 (170-150), general anaesthesia with regional: 40 (8-76)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 surgical procedure changed, 1 protocol not followed; Group 2 Number missing: 1, Reason: 1 surgical procedure changed,

Protocol outcome 4: Length of stay at .
- Actual outcome: Median length of stay at .; Median (range) in days: general anaesthesia with LIA: 2 (1-6), general anaesthesia with regional: 2 (1-3)
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low,

Study	Bjornholdt 2015[10]
Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 surgical procedure changed, 1 protocol not followed; Group 2 Number missing: 1, Reason: 1 surgical procedure changed,	
Protocol outcomes not reported by the study	Mortality at within 90 days; Quality of life at within 30 days; Postoperative pain at within 30 days; Postoperative neurocognitive decline at within 30 days; Hospital readmissions at within 30 days; Adverse events: brachial plexus injury at within 90 days of surgery; Nausea at within 30 days; Mobilisation (ambulation) within 24 hours after surgery at .

Study	Ding 2017[18]
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=1824)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 90 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Retrospective propensity-matched cohort from 4158 people using nearest-neighbor matching and including a total of 26 covariates. People who had total shoulder arthroplasty who received either general anaesthesia with or without nerve blockade or regional anaesthesia alone.
Exclusion criteria	People with previous upper extremity arthroplasty, fracture related diagnosis, surgery for prior infection, tumour or those with previous surgical complications.
Recruitment/selection of patients	Included in New York Statewide Planning and Research Cooperative System (SPARCS) database
Age, gender and ethnicity	Age - Mean (SD): 68 (10). Gender (M:F): 828/996. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear 3. Form of shoulder replacement:: (Anatomical total or reverse total arthroplasty).
Indirectness of population	No indirectness
Interventions	(n=912) Intervention 1: General and regional - General anaesthesia with or without regional blockade. General anaesthesia with or without regional blockade. . Duration Surgery and in hospital period. Concurrent medication/care: Unclear. Indirectness: No indirectness (n=912) Intervention 2: Regional - Regional anaesthesia. Regional anaesthesia. Duration Surgery and in-hospital period. Concurrent medication/care: Not detailed. Indirectness: No indirectness
Funding	No funding ("The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article")
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA versus GENERAL ANAESTHESIA WITH OR WITHOUT REGIONAL BLOCKADE	

Protocol outcome 1: Thromboembolic complications at within 90 days - Actual outcome: DVT or PE at In hospital; Group 1: 2/912, Group 2: 1/912 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Hospital readmissions at within 30 days - Actual outcome: Readmission at Within 90 days; Group 1: 38/912, Group 2: 59/912; Comments: odds ratio of 1.59 (1.05–2.42, p < 0.001). Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 2.3 days (SD 0.9); n=912, Group 2: mean 2 days (SD 1.3); n=912 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Nausea at within 30 days - Actual outcome: Gastrointestinal complications at In hospital; Group 1: 0/912, Group 2: 0/912 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at within 90 days; Quality of life at within 30 days; Postoperative pain at within 30 days; Postoperative neurocognitive decline at within 30 days; Adverse events: phrenic nerve injury at within 90 days of surgery; Adverse events: brachial plexus injury at within 90 days of surgery; Postoperative use of analgesia at as reported; Mobilisation (ambulation) within 24 hours after surgery at .

Study	Namdari 2017[61]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=156)
Countries and setting	Conducted in USA; Setting: Single hospital. Surgery performed by 1 of 4 shoulder surgeons.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 24 hours follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis or rotator cuff tear arthropathy undergoing conventional or reverse total shoulder arthroplasty.
Exclusion criteria	People with psychiatric illness, revision arthroplasty, diagnosis of fracture, workers compensation or disability or litigation claim, unable to consent, known adverse reactions or allergy to study medications, chronic pain syndromes, taking long acting pain medications, hepatic disease.
Age, gender and ethnicity	Age - Mean (SD): 71 (9) and 68 (8). Gender (M:F): 71/85. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear 3. Form of shoulder replacement:: Mixed (Anatomical and reverse).
Indirectness of population	No indirectness
Interventions	(n=78) Intervention 1: General - General anaesthesia with local infiltration analgesia (LIA). General anaesthesia (no details). Intraoperative LIA with bupivacaine liposome in Exparel suspension. Injections into anterior capsule, subscapularis, deltoid, pectoralis major, and subcutaneous fat layer. . Duration Surgery. Concurrent medication/care: No preoperative oral analgesic regimen utilised. Intraoperative narcotic administration at the discretion of the anaesthetist. PCA with morphine or fentanyl used where required. . Indirectness: No indirectness (n=78) Intervention 2: General and regional - General anaesthesia with regional anaesthesia (ultrasound guided ISB or other supraclavicular brachial plexus block). General anaesthesia (no details). Preoperative ultrasound guided interscalene brachial plexus blockade using ropivacaine. . Duration Surgery. Concurrent medication/care: No preoperative oral analgesic regimen utilised. Intraoperative narcotic administration at the discretion of the anaesthetist. PCA with morphine or fentanyl used where required.. Indirectness: No indirectness
Funding	No funding (No external funding)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (LIA) versus GENERAL ANAESTHESIA WITH REGIONAL ANAESTHESIA (ULTRASOUND GUIDED ISB OR OTHER SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK)

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain at 8 hours after surgery; Group 1: mean 3.2 (SD 2.2); n=78, Group 2: mean 1.4 (SD 2.4); n=78; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Postoperative narcotic consumption at 24 hours after surgery; Group 1: mean 14.4 morphine equivalent units (SD 16.8); n=78, Group 2: mean 14.8 morphine equivalent units (SD 11.3); n=78
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at .
- Actual outcome: Hospital length of stay at .; Group 1: mean 1.6 days (SD 0.8); n=78, Group 2: mean 1.8 days (SD 0.6); n=78
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality at within 90 days; Quality of life at within 30 days; Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days; Adverse events: phrenic nerve injury at within 90 days of surgery; Adverse events: brachial plexus injury at within 90 days of surgery; Nausea at within 30 days; Mobilisation (ambulation) within 24 hours after surgery at .

Study	Okoroha 2016[66]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=57)
Countries and setting	Conducted in USA; Setting: Operated on by 1 of 3 surgeons.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 4 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults undergoing primary shoulder replacement surgery.
Exclusion criteria	Known allergy or intolerance to dexamethasone, ropivacaine, or bupivacaine. Substantial alcohol or drug abuse. Pregnancy.
Recruitment/selection of patients	October 2015 to June 2015.
Age, gender and ethnicity	Age - Mean (range): 67 (49-86) and 69 (50-74). Gender (M:F): 28/29. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear 3. Form of shoulder replacement:: Mixed (Anatomic or reverse.).
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: General and regional - General anaesthesia with regional anaesthesia (ultrasound guided ISB or other supraclavicular brachial plexus block). General anaesthesia (no details). Single dose interscalene nerve block 1 hour before surgery using ropivacaine. . Duration Surgery. Concurrent medication/care: Standardised postoperative pain regimen consisting of acetaminophe with oxycodone and morphine as required. . Indirectness: No indirectness (n=26) Intervention 2: General - General anaesthesia with local infiltration analgesia (LIA). General anaesthesia (no details). LIA using lipsomal bupivacaine in saline. Injected into deltoid, pectoralis, periosteum, and along the incision before closure. . Duration Surgery. Concurrent medication/care: Standardised postoperative pain regimen consisting of acetaminophe with oxycodone and morphine as required. . Indirectness: No indirectness
Funding	Funding not stated (However it was declared authors had no conflicts of interest related to the paper)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (LIA) versus GENERAL ANAESTHESIA WITH REGIONAL ANAESTHESIA (ULTRASOUND GUIDED ISB OR OTHER SUPRACLAVICULAR BRACHIAL

PLEXUS BLOCK) Protocol outcome 1: Postoperative pain at within 30 days - Actual outcome: Mean pain score at On the day of surgery; Group 1: mean 4.8 (SD 1.8); n=26, Group 2: mean 4 (SD 1.8); n=31; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA not reported; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Adverse events: phrenic nerve injury at within 90 days of surgery - Actual outcome: Phrenic nerve palsy requiring readmission at Unclear; Group 1: 0/26, Group 2: 1/31 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA not reported; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Postoperative use of analgesia at as reported - Actual outcome: Opioid requirements at In the 24 hours after surgery; Group 1: mean 14.8 IV morphine equivalents (SD 9.2); n=26, Group 2: mean 21.4 IV morphine equivalents (SD 11.3); n=31 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA not reported; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 1.5 days (SD 1); n=26, Group 2: mean 1.5 days (SD 1); n=31 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA not reported; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at within 90 days; Quality of life at within 30 days; Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days; Adverse events: brachial plexus injury at within 90 days of surgery; Nausea at within 30 days; Mobilisation (ambulation) within 24 hours after surgery at .

Study	Stundner 2014[81]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=17157)
Countries and setting	Conducted in USA; Setting: It includes hospitals with diverse geographical locations across the United States, different sizes, urban/rural settings, and teaching status. Medicare, Medicaid, and uninsured patients are captured in the database, as well as those with commercial insurance.
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery and in-hospital period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who had a total shoulder arthroplasty. This data came from the Premier database. This is an administrative database containing discharge information from about 400 acute-care hospitals throughout the United States, covering about 20% of all discharges in the United States from this time period.The ICD-9-CM code (81.80) with subcodes for general anaesthesia was used to find the population.
Exclusion criteria	None detailed
Age, gender and ethnicity	Age - Other: Mean (95% CI) 69 (68-69) and 69 (69-69). Gender (M:F): 7704/9853. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear 3. Form of shoulder replacement:: Not stated / Unclear (Certainly total shoulder arthorplasty but anatomical or reverse not stated.).
Extra comments	All models controlled for age group, gender, ethnicity, Deyo index (0, 1, 2, 3+), and presence of sleep apnea and obesity.
Indirectness of population	No indirectness
Interventions	(n=13892) Intervention 1: General - General anaesthesia. General anaesthesia. Duration In-hospital period. Concurrent medication/care: Not detailed. Indirectness: No indirectness (n=3665) Intervention 2: General and regional - General anaesthesia with peripheral nerve block. General anesthesia with an upper-extremity nerve block. Duration In-hospital period. Concurrent medication/care: Not detailed. Indirectness: No indirectness
Funding	No funding (Each author certifies that he or she, or a member of his or her immediate family, has no commercial associations that might pose a conflict of interest in connection with the submitted paper)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL ANAESTHESIA WITH PERIPHERAL NERVE BLOCK versus

GENERAL ANAESTHESIA Protocol outcome 1: Thromboembolic complications at within 90 days - Actual outcome: Pulmonary complications: pulmonary embolism, pneumonia, and pulmonary compromise. at During hospital stay; OR; 0.87 (95%CI 0.66 to 1.16, Comments: Results are from the multivariable logistic regression model adjusted for age group, sex, ethnicity, Deyo (comorbidity) index, presence of sleep apnea and morbid obesity.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Hospital readmissions at within 30 days - Actual outcome: Intensive care unit admission at Unclear; OR; 1.16 (95%CI 0.93 to 1.46, Comments: Results are from the multivariable logistic regression model adjusted for age group, sex, ethnicity, Deyo (comorbidity) index, presence of sleep apnea and morbid obesity.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Length of stay at . - Actual outcome: Length of stay at .; OR; 0.89 (95%CI 0.82 to 0.97, Comments: Results are from the multivariable logistic regression model adjusted for age group, sex, ethnicity, Deyo (comorbidity) index, presence of sleep apnea and morbid obesity.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at within 90 days; Quality of life at within 30 days; Postoperative pain at within 30 days; Postoperative neurocognitive decline at within 30 days; Adverse events: phrenic nerve injury at within 90 days of surgery; Adverse events: brachial plexus injury at within 90 days of surgery; Postoperative use of analgesia at as reported; Nausea at within 30 days; Mobilisation (ambulation) within 24 hours after surgery at.

Appendix E: Forest plots

E.1 General anaesthesia with LIA versus general anaesthesia with regional anaesthesia

Figure 2: Postoperative pain

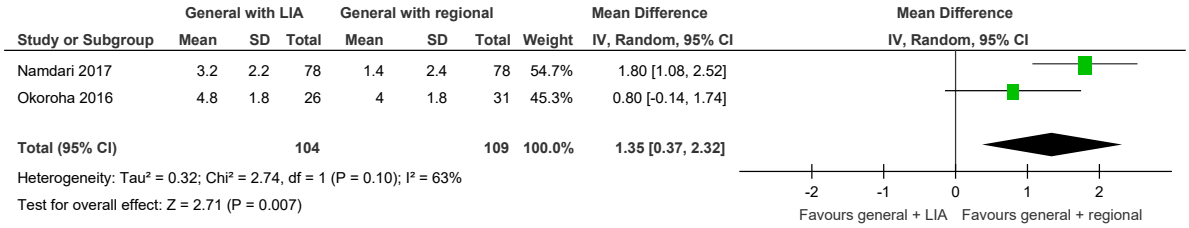


Figure 3: Thromboembolic complications

Figure 4: Phrenic nerve palsy

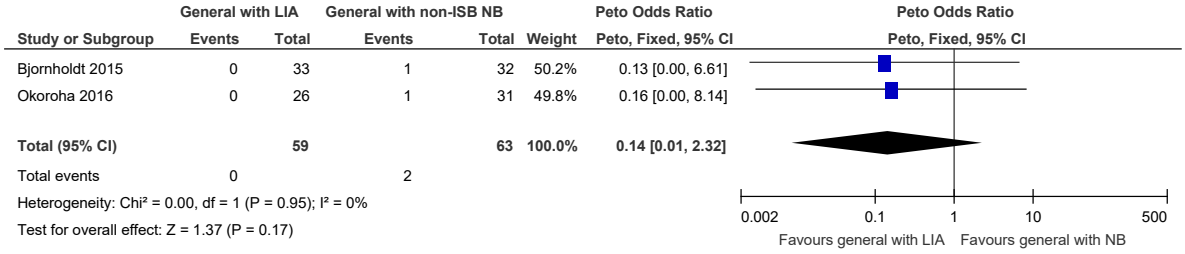


Figure 5: Postoperative use of analgesia

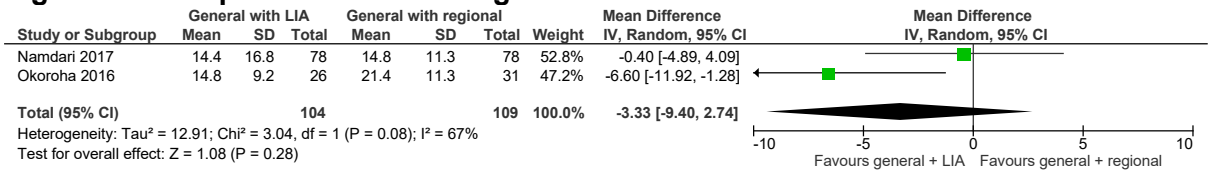
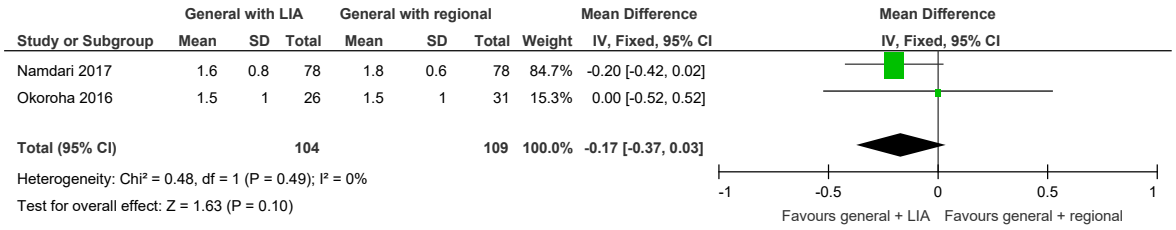


Figure 6: Length of stay



General anaesthesia with LIA versus general anaesthesia

E.2 Regional anaesthesia versus general anaesthesia with or without regional blockade

Figure 7: Readmission within 90 days

Figure 8: Gastrointestinal complications

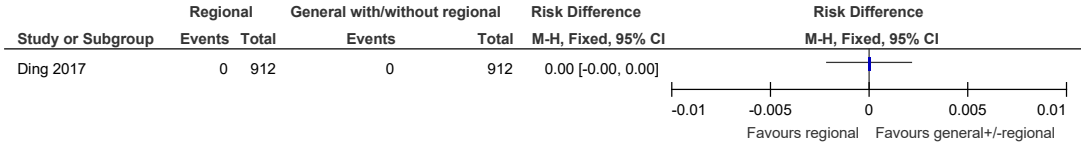


Figure 9: Thromboembolic complications

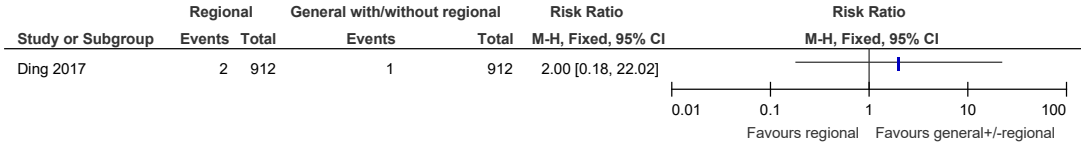
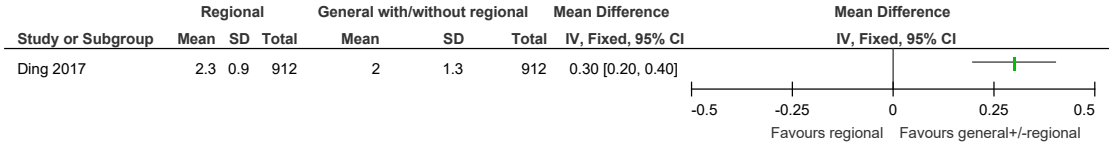


Figure 10: Length of stay



E.3 General anaesthesia with peripheral nerve block versus general anaesthesia

Figure 11: Intensive care unit admission

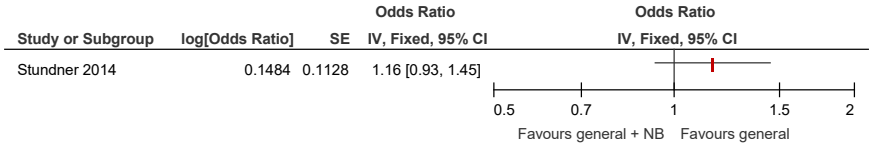


Figure 12: Pulmonary complications

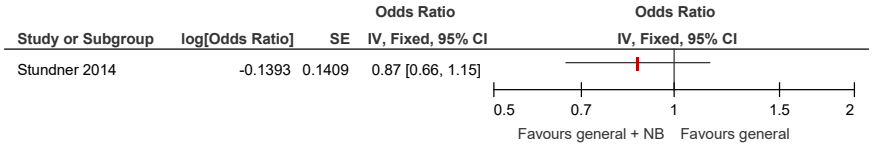
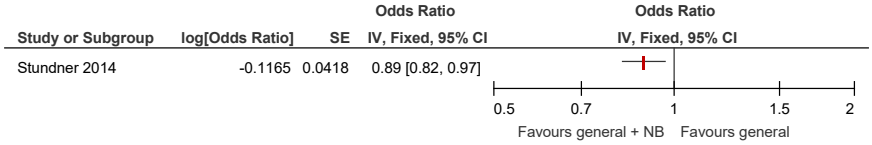


Figure 13: Increased length of stay



Appendix F: GRADE tables

Table 11: RCT evidence profile: General anaesthesia with LIA versus general anaesthesia with regional anaesthesia

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General anaesthesia with LIA	General anaesthesia with regional anaesthesia	Relative (95% CI)	Absolute		
Postoperative pain (measured with: Mean VAS; range of scores: 0-10; Better indicated by lower values)												
2	randomised trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	none	104	109	-	MD 1.35 higher (0.37 to 2.32 higher)	⊕OOO VERY LOW	CRITICAL
Thromboembolic complications (assessed with: Pulmonary embolism)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/33 (0%)	1/32 (3.1%)	OR 0.13 (0 to 6.61)	27 fewer per 1000 (from 31 fewer to 145 more)	⊕OOO VERY LOW	CRITICAL
Phrenic nerve palsy (assessed with: Suspected or requiring readmission)												
2	randomised	serious[1]	no serious	no serious	very serious[3]	none	0/59	2/63	OR 0.14 (0.01 to	27 fewer per 1000 (from 31 fewer to	⊕OOO	CRITICAL

	trials		inconsistency	indirectness			(0%)	(3.2%)	2.32)	39 more)	VERY LOW	
Postoperative use of analgesia (measured with: Narcotic consumption; Better indicated by lower values)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	104	109	-	MD 3.33 lower (9.04 lower to 2.74 higher)	⊕OOO VERY LOW	IMPORTANT
Postoperative use of analgesia[4] (assessed with: Median opioid consumption)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Unclear	none	Median (IQR) in mg General anaesthesia with LIA: 95 (170-150) General anaesthesia with non-ISB nerve block: 40 (8-76)	Not estimable	Not estimable	Deemed to be at very high risk of bias. Imprecision unclear.	Unable to assess	IMPORTANT
Length of stay (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	104	109	-	MD 0.17 lower (0.37 lower to 0.03 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Median length of stay[4]												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Unclear	none	Median (range) in days General	Not estimable	Not estimable	Deemed to be at very high risk of bias. Imprecision	Unable to assess	IMPORTANT

							anaesthesia with LIA: 2 (1-6) General anaesthesia with non-ISB nerve block: 2 (1-3)			unclear.		

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Outcome reported as a median and it was not possible to assess the precision or to calculate the absolute effect and therefore grade the overall quality.

4 Outcome reported as a median and it was not possible to assess the precision or to calculate the absolute effect.

Table 12: NRS evidence profile: Regional anaesthesia versus general anaesthesia with or without regional blockade

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Regional anaesthesia**	**General anaesthesia with or without regional blockade**	**Relative (95% CI)**	**Absolute**		
Readmission												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38/912 (4.2%)	59/912 (6.5%)	RR 0.64 (0.43 to 0.96)	23 fewer per 1000 (from 3 fewer to 37 fewer)	⊕OOO VERY LOW	CRITICAL
Thromboembolic complications (assessed with: DVT or PE)												

1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/912 (0.22%)	1/912 (0.11%)	RR 2 (0.18 to 22.02)	1 more per 1000 (from 1 fewer to 23 more)	⊕OOO VERY LOW	CRITICAL
Length of stay (Better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	912	912	-	MD 0.3 higher (0.2 to 0.4 higher)	⊕OOO VERY LOW	IMPORTANT
Nausea (assessed with: gastrointestinal complications)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/912 (0%)	0/912 (0%)	RD 0 (0 to 0)	0 fewer per 1000 (from 0 more to 0 more)[3]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effect calculated using the risk difference. RD: 0 (0-0)

Table 13: NRS evidence profile: General anaesthesia with peripheral nerve block versus general anaesthesia

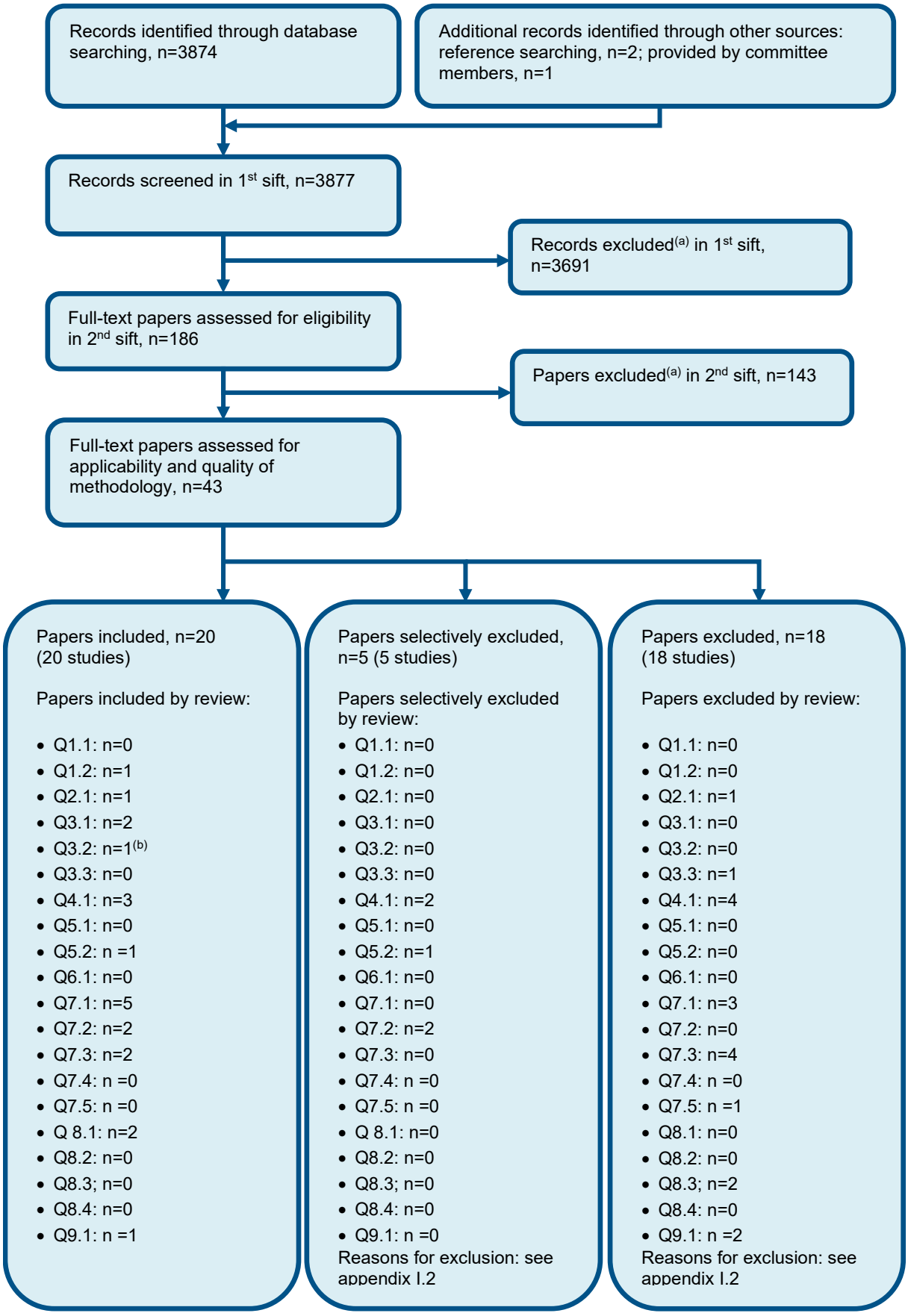
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**General anaesthesia with peripheral nerve block**	**General anaesthesia**	**Relative (95% CI)**	**Absolute**		
Intensive care unit admission												

1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	Not estimable	Not estimable	OR 1.16 (0.93 to 1.45)	Not estimable	⊕OOO VERY LOW	CRITICAL
Pulmonary complications (assessed with: pulmonary embolism, pneumonia, and pulmonary compromise)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	Not estimable	Not estimable	OR 0 (0.66 to 1.15)	Not estimable	⊕OOO VERY LOW	CRITICAL
Increased length of stay												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3665	13892	OR 0.89 (0.82 to 0.97)	Not estimable	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Appendix G: Health economic evidence selection

Figure 14: Flow chart of health economic study selection for the guideline



a) Non-relevant population, intervention, comparison, design or setting; non-English language
b) One study was applicable to both Q3.1 and Q3.2

Appendix H: Health economic evidence tables

No studies were found

Appendix I: Nerve block threshold analysis

A threshold analysis was conducted in order to determine the likelihood of the addition of nerve block to any anaesthetic regimen being cost effective. The analysis was deemed necessary by the committee given the lack of health economic evidence about the addition of nerve block.

I.1 Method

The analysis uses estimates of incremental cost to find what QALY or health related quality of life (HRQoL) gain is required at a given threshold of cost effectiveness. The threshold selected for this analysis was £20,000 in line with the NICE reference case. A range of incremental costs (see Table 14) driven by the time required to administer the nerve block (30 minutes, 10 minutes and 5 minutes) and if the cost of theatre time was incorporated (yes or no) were included in the analysis. The rationale for having theatre time included as a cost variable was that the committee suggested that if 2 anaesthetists are available a nerve block can be administered in the anaesthesia room, not incurring additional theatre time costs. Therefore, for scenarios where theatre time was not included, 2 consultant anaesthetists were costed in. Whereas when theatre time was included, only one consultant anaesthetist was costed in. The time required to administer a nerve block reflected the experience of the staff member in giving it, a quicker time equates to a more experienced staff member. These factors were investigated in line with the committee's agreement that they were variable in current practice. Other resources used for nerve block administration were taken from CG124[64] and agreed by the committee.

The different incremental cost estimates were substituted into the equation for the incremental cost-effectiveness ratio (ICER). The equation was then rearranged (see equation below) to find the incremental QALY gain needed for the nerve block intervention to be cost effective at £20,000.

$$ICER = Incremental\ costs \div Incremental\ QALY$$

Therefore:

$$Incremental\ QALY = Incremental\ costs \div ICER$$

Following this an additional factor was analysed that was deemed variable by the committee; the time that nerve blocks have an effect upon people. The committee suggested that it could be argued the effect ranges from a matter of hours to a lifetime. The analgesic effect of a nerve block is variable but may be up to 18 hours for shoulder replacements. However, a 24 hour time horizon may be the most appropriate when considering acute post-operative outcomes (for example, pain, post-operative nausea and vomiting). A longer time horizon of 10 days to 30 days may be most appropriate to account for the possible effect of anaesthetic choice on adverse clinical outcomes (for example post-operative morbidity and mortality). Lastly, an even longer time horizon would be needed to account for long term outcomes (such as chronic pain, opioid dependence and range of motion). However, in line with the pain score outcome included in the protocol, the maximum effect horizon included in the analysis was 30 days. The different QALY gains calculated as outlined above were then substituted into the QALY equation with the different time horizons (24 hours, 3 days, 10 days and 30 days). The equation was then rearranged to find the gain in HRQoL gain needed to be cost effective at a threshold of £20,000 under each scenario.

$$Incremental\ QALY = Incremental\ life\ years\ gained \times Incremental\ utility\ (\text{HRQoL})$$

Therefore:

*Incremental utility (*HRQoL *) = Incremental QALY ÷ Incremental Life years gained*

If the requisite HRQoL gain was greater than 1, then it was deemed not possible for the addition of nerve blocks to be cost effective under that scenario. The assumed scale of health related quality of life was 0 to 1 where 1 is the maximum health related quality of life and 0 the least. This was chosen as the NICE Reference case states to use the EQ-5D instrument that also uses a 0 to 1 scale. The smaller the gain needed in HRQoL, the more likely the addition of nerve block was to be cost effective.

Table 14 shows the unit costs used to calculate the cost for the addition of a nerve block to an anaesthetic regimen for a the different scenarios likely to represent current practice ion the NHS

Table 14: UK 2018 cost for the addition of a nerve block to an anaesthetic regimen for primary elective joint replacement when varying administration time and the inclusion of theatre time cost

Extra time in theatre	Resource	Unit cost	Source
5 min	Biogel	£1.07	NHS Hospital
	Chlorhexidine	£1.08	NHS Hospital
	Vial with Lidocaine 1% 10ml ampoule	£0.38	BNF
	Vial of 0.5% Levobupivacaine (5mg/ml)	£3.88	BNF
	Syringes (10ml)	£0.06	NHS Hospital
	Filter needle	£0.23	NHS Hospital
	Regional block needle	£5.78	NHS Hospital
	Hypodermic needle	£1.35	NHS Hospital
	Cost per consultant anaesthetist (£1.80 per minute)	£9.00	PSSRU 2018
	Total cost excluding theatre time[(a)]	**£31.83**	
	Cost of theatre time (£20.50 per min)	£102.50	CG124
	Total cost including theatre time[(b)]	**£125.33**	
10 min	Biogel	£1.07	NHS Hospital
	Chlorhexidine	£1.08	NHS Hospital
	Vial with Lidocaine 1% 10ml ampoule	£0.38	BNF
	Vial of 0.5% Levobupivacaine (5mg/ml)	£3.88	BNF
	Syringes (10ml)	£0.06	NHS Hospital
	Filter needle	£0.23	NHS Hospital
	Regional block needle	£5.78	NHS Hospital
	Hypodermic needle	£1.35	NHS Hospital
	Cost per consultant anaesthetist (£1.80 per minute)	£18.00	PSSRU 2018
	Total cost excluding theatre time[(a)]	**£49.83**	
	Cost of theatre time (£20.50 per min)	£205.00	CG124
	Total cost including theatre time[(b)]	**£236.83**	NHS Hospital
30 min	Biogel	£1.07	NHS Hospital

	Chlorhexidine	£1.08	NHS Hospital
	Vial with Lidocaine 1% 10ml ampoule	£0.38	BNF
	Vial of 0.5% Levobupivacaine (5mg/ml)	£3.88	BNF
	Syringes (10ml)	£0.06	NHS Hospital
	Filter needle	£0.23	NHS Hospital
	Regional block needle	£5.78	NHS Hospital
	Hypodermic needle	£1.35	NHS Hospital
	Cost per consultant anaesthetist (£1.80 per minute)	£54.00	PSSRU 2018
	Total cost excluding theatre time[(a)]	**£121.83**	
	Cost of theatre time (£20.50 per min)	£615.00	CG124
	Total cost including theatre time[(b)]	**£682.83**	NHS Hospital

Source: PSSRU (Personal Social Services Research Unit)[15]; CG124[64]

(a) Total costs excluding theatre time included the cost of 2 anaesthetists

(b) It was assumed that the cost of theatre time from CG124 did not include personnel costs

(c) NHS hospital is Peterborough and Stamford Hospitals NHS Foundation Trust which provided information for CG124[64]

I.2 Results

The gain in QALY and gain in HRQoL needed under a range of different scenarios is shown in Table 15. For a number of scenarios; particularly when the time to administer was 30 minutes, the intervention effect was 24 hours and when theatre time was included; the likelihood of nerve blocks being cost effective was impossible given that the gain in HRQoL needed was greater than 1. When the assumptions were softened to the middle values, the gain in HRQoL was often not impossible (the gain needed was less than 1) but improbable. Finally, when time to administer was 5 minutes, the intervention effect was 30 days and when theatre time was excluded, the gain in HRQoL and therefore cost-effectiveness was more realistic.

Table 15: Threshold analysis results

Time to add nerve block	Theatre time included	Incremental cost	Gain in QALY needed	Health related quality of life gain needed in:			
				24 hours	3 days	10 days	30 days
30 mins	Yes	£682.83	0.034	12.462	4.154	1.246	0.415
10 mins	Yes	£236.83	0.012	4.322	1.441	0.432	0.144
5 mins	Yes	£125.33	0.006	2.287	0.762	0.229	0.076
30 mins	No	£121.83	0.006	2.223	0.741	0.222	0.074
10 mins	No	£49.83	0.002	0.909	0.303	0.091	0.030

Time to add nerve block	Theatre time included	Incremental cost	Gain in QALY needed	Health related quality of life gain needed in:			
				24 hours	3 days	10 days	30 days
5 mins	No	£31.83	0.002	0.581	0.194	0.058	0.019

I.3 Conclusions

The results indicated that for some scenarios it is impossible for nerve blocks to be cost effective, for others cost effectiveness is improbable, whilst for some it is possible. Due to the lack of clinical evidence and uncertainty regarding cost effectiveness shown by this threshold analysis they made 2 research recommendations. One of these was to explore the clinical and cost effectiveness of supplementing general anaesthesia with a nerve block or LIA for shoulder replacement surgery. The second was to explore the clinical and cost effectiveness of regional and/or general anaesthesia for shoulder replacement surgery.

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 16: Studies excluded from the clinical review

Study	Exclusion reason
Abildgaard 2017[1]	Incorrect interventions
Aksu 2015[2]	Not review population
Angerame 2017[3]	Observational study without adjustment for confounding factors
Atchabahian 2015[4]	Systematic review with different inclusion criteria however included studies were checked for this review
Auyong 2017[5]	Inappropriate comparison
Axelsson 2008[6]	Not review population
Balocco 2018[7]	Review of bupivacaine formulations
Beaudet 2008[8]	Not review population
Bishop 2005[9]	Not review population
Boddu 2018[11]	Observational study without adjustment for confounding factors
Cao 2017[12]	Systematic review with different inclusion criteria however included studies were checked for this review
Choi 2008[13]	Not in English
Codding 2018[14]	Overview of anaesthesia for shoulder surgery
Desmet 2013[16]	Not review population
Desmet 2015[17]	Not review population
Dorman 1994[19]	Not review population
Ekatodramis 2003[20]	Not review population
Eroglu 2004[21]	Not review population
Flory 1995[22]	Not review population
Gabriel 2017[23]	Unclear if the study population is people undergoing primary knee arthroplasty
Ghaleb 2004[24]	Overview of anaesthesia for shoulder surgery
Goebel 2010[25]	Not review population
Gohl 2001[26]	Not review population
Gottschalk 2003[27]	Not review population
Grossi 1998[28]	Not review population
Guo 2017[29]	Systematic review with different inclusion criteria however included studies were checked for this review
Gwam 2017[30]	Knee arthroplasty study
Haasio 1990[31]	Not review population
Hamdani 2014[32]	Not review population
Hannan 2016[34]	Observational study without adjustment for confounding factors
Herrick 2018[35]	Included people having revision arthroplasty
Hofmann-kiefer 2008[36]	Not review population
Hong 2003[37]	Not review population
Huang 2017[38]	Review of shoulder analgesia
Ikemoto 2010[39]	Not review population
Ilfeld 2003[40]	Not review population
Ilfeld 2004[41]	Not review population

Study	Exclusion reason
Ilfeld 2006[42]	Includes people undergoing revision shoulder replacement surgery
Im 2007[43]	Not in English
Jochum 1997[44]	Not in English
Kahn 1999[45]	Not review population
Kim 2017[46]	Not review population
Kinnard 1994[48]	Conference abstract
Kinnard 1995[47]	Not review population
Kocamanoğlu 2005[49]	Not in English
Kostadinova 2009[50]	Unable to obtain
Krone 2001[51]	Not review population
Lee 2010[52]	Not in English
Lehmann 2015[53]	Not review population
Lehtipalo 1999[54]	Not review population
Mahmoodpoor 2011[55]	Not review population
Mariano 2009[56]	Not review population
Mclaughlin 2018[58]	Included people having revision arthroplasty
Mueller 2017[59]	Included people having revision arthroplasty
Muittari 1998[60]	Not review population
Namdari 2018[62]	Incorrect interventions
Niiya 2010[65]	Not in English
Park 2006[67]	Not in English
Pearson 2015[68]	Not review population
Pere 1993[69]	Not review population
Renes 2009[70]	Not review population
Rosenfeld 2016[71]	Not review population
Routman 2017[72]	Observational study without adjustment for confounding factors
Sabesan 2017[73]	Inappropriate comparison
Sermeus 2016[74]	Not review population
Sicard 2019[75]	Incorrect interventions
Singelyn 1999[76]	Not review population
Soeding 2013[77]	Not review population
Song 2011[78]	Not review population
Stevens 2007[79]	Not review population
Stundner 2016[80]	Not review population
Sun 2018[82]	Systematic review with different inclusion criteria however included studies were checked for this review
Tamosiūnas 2004[83]	Not in English
Tantry 2016[84]	Not review population
Tashjian 2016[85]	Included people having revision arthroplasty
Tetzlaff 1995[86]	Not review population
Trabelsi 2015[88]	Unable to obtain
Trabelsi 2017[87]	Not review population
Tran 2017[89]	Review of diaphragm sparing nerve blocks
Ullah 2014[90]	Systematic review with different inclusion criteria however included studies were checked for this review
Verelst 2013[91]	Review of analgesic strategies

Study	Exclusion reason
Vorobeichik 2018[92]	Systematic review with different inclusion criteria however included studies were checked for this review
Warrender 2017[93]	Systematic review with a different population.
Weller 2017[94]	Observational study without adjustment for confounding factors
Wiegel 2017[95]	Unable to obtain
Wiesmann 2016[96]	Not review population
Wurm 2003[97]	Not review population
Yadeau 2016[98]	Inappropriate comparison
Yan 2017[99]	Systematic review with different inclusion criteria however included studies were checked for this review
Yang 2010[101]	Not review population
Yang 2013[100]	Not review population

J.2 Excluded health economic studies

Table 17: Studies excluded from the health economic review

Reference	Reason for exclusion
Hamilton 2019[33]	No intraoperative costs were captured

Appendix K: Research recommendations

K.1 Supplementary anaesthesia in elective shoulder replacement

Research question: In adults having elective shoulder joint replacement with general anaesthesia, what is the clinical and cost effectiveness of supplementary local infiltration anaesthesia compared with a supplementary nerve block?

Why this is important:

The number of people having shoulder replacement surgery is increasing year on year with over 6,500 people having their shoulder replaced in the UK in 2017. Most of these are elective procedures. There have been recent changes and variations in practice around which type of anaesthesia might offer the best outcomes for different patient groups. There is a cost implication with the type of anaesthesia used due to the time taken to carry out the different modes of anaesthesia.

PICO question	Population: People undergoing primary shoulder replacement surgery Intervention(s): • General anaesthesia with LIA • General anaesthesia with nerve blocks • General anaesthesia with regional anaesthesia Comparison: a comparison of interventions Outcome(s): Transfusion rates, length of stay, post-operative analgesia requirements, postoperative pain, Patient Reported Outcome Measures (PROMs)
Study design	RCT
Other details	Time taken for regional blocks to be enacted can be between 5 mins to 30 minutes based on experience of anaesthetist carrying out procedure. This has a cost implications to the NHS

Appendix L:Research recommendations

L.1 Regional compared with general anaesthesia or a combination in elective shoulder replacement

Research question: In adults having elective shoulder joint replacement, what is the relative clinical and cost effectiveness of general anaesthesia, regional anaesthesia, and general combined with regional anaesthesia?

Why this is important:

The number of people having shoulder replacement surgery is increasing year on year with over 6,500 people having their shoulder replaced in the UK in 2017. Most of these are elective procedures. There have been recent changes and variations in practice around which type of anaesthesia might offer the best outcomes for different patient groups. The implications of utilising regional anaesthesia alone is to facilitate day-case shoulder replacement surgery in the NHS.

PICO question	Population: People undergoing primary shoulder replacement surgery Intervention(s): • General anaesthesia • Regional anaesthesia • General anaesthesia with regional anaesthesia Comparison: a comparison of interventions Outcome(s): Transfusion rates, length of stay, post-operative analgesia requirements, postoperative pain, Patient Reported Outcome Measures (PROMs)
Study design	RCT
Other details	• No existing national priorities. • Day case joint replacement would be important to patients as reduced length of stay is thought to increase person's wellbeing. • This would inform future NICE guidance on anaesthesia for primary shoulder replacement surgery.