National Institute for Health and Care Excellence

Final

Joint replacement (primary): hip, knee and shoulder

[D] Evidence review for anaesthesia for hip replacement

NICE guideline NG157

Intervention evidence review underpinning recommendation 1.3.1 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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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

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1 Anaesthesia for elective hip joint replacement

1.1 Review question: In adults having primary elective hip joint replacement, what is the clinical and cost effectiveness of intraoperative anaesthetic approaches: regional anaesthesia or general anaesthesia, with or without nerve blocks and local infiltration analgesia, compared with each other or in combination?

1.2 Introduction

Total hip replacement surgery is painful. The anaesthetist and person undergoing surgery can choose from a number of interventions which aim to minimise this.

Firstly there is a choice of underlying anaesthesia and the options are general anaesthesia, regional anaesthesia, or a combination of both. General anaesthesia is where the patient is put into a deep sleep. Regional anaesthesia is where only part of the body is anaesthetised, using local anaesthetic to 'turn off' the nerves temporarily. During this time, the patient is typically aware of some pushing or pulling, but no pain.

Once it has been decided whether to use general, regional anaesthesia or both, then the technique or combination of techniques, needed to prevent pain after the operation should be considered. Preventing early pain is important in itself and, it is also recognised that reducing pain in the first few hours after surgery may help reduce pain over a longer period.

There are 2 supplementary anaesthetic options that can be utilised. Firstly, local anaesthetic infiltration where a large volume of anaesthetic is injected into the tissues around the operation site. This technique typically lasts for 8 to 10 hours. A second approach is to target an injection of anaesthetic to the nerves that supply the hip joint, often using an ultrasound machine to identify the nerve. Local anaesthetic infiltration and nerve blocks can be performed separately, or together.

This review seeks to determine the most clinically effective and cost-effective approach to both types of anaesthetic, and the type of supplementary anaesthetic options for total hip replacement.

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 hip joint replacement
Interventions	• General anaesthesia • General anaesthesia with nerve block • General anaesthesia with local infiltration analgesia (during or after procedure) • General anaesthesia with nerve block and local infiltration analgesia (during or after procedure)

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	• Regional anaesthesia • Regional anaesthesia with nerve block • Regional anaesthesia with local infiltration analgesia (during or after surgery) • Regional anaesthesia with nerve block and local infiltration analgesia (during or after surgery) • General and regional anaesthesia • General and regional anaesthesia with nerve block • General and regional anaesthesia with local infiltration analgesia (during or after procedure) • General and regional anaesthesia with nerve block and local infiltration analgesia (during or after procedure)
Comparison	Comparison of interventions
Outcomes	**Critical** • Mortality: within 90 days (dichotomous) • Quality of life within 30 days (continuous) • Postoperative pain within 30 days (continuous) • Postoperative neurocognitive decline within 30 days (dichotomous) • Thromboembolic complications within 90 days (VTE; dichotomous) • Hospital readmission within 30 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 hip joint replacement surgery.

Twenty four RCTs and five observational studies were included in the review;[18, 40, 56, 61, 62, 64, 66, 69, 89-91, 96, 97, 101, 102, 105, 132, 133, 140, 143, 151, 162, 165, 171, 222, 224, 230, 236, 238] these are summarised in Table 2 below. The RCTs were too small to accurately assess an outcome as rare as mortality and this was thought to be a key difference between regional anaesthesia and general anaesthesia. Therefore observational studies were included for the mortality within 90 days outcome for the regional anaesthesia versus general anaesthesia comparison. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). See also the study selection flow chart in Appendix C: study evidence tables in Appendix D: forest plots in Appendix E: and GRADE tables in Appendix H:

1.4.2 Excluded studies

See the excluded studies list in Appendix I:

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Details of interventions	Population	Outcomes	Comments
Regional anaesthesia with LIA versus regional anaesthesia (RCTs)				
Den hartog 2015[56]	All people had spinal anaesthesia using bupivacaine and propofol used for sedation. LIA was done with ropivacaine and adrenaline. There were two LIA groups, one utilising "reverse" LIA. Those not in the LIA groups received a placebo LIA with saline.	People with osteoarthritis of the hip and ASA I-II for whom primary THA has been recommended. Mean (range) age: 64 (43-84) and 69 (49-85) and 68 (55-84) N=75	• Number of people with postoperative use of analgesia • Nausea within 30 days	Netherlands
Dobie 2012[61]	All people had spinal anaesthesia. The LIA group received LIA before wound closure. A solution of levobupivacaine with adrenaline in saline was utilised. 160ml of this mixture was infiltrated into soft tissues.	People with degenerative or rheumatoid arthritis undergoing primary THA. ASA: I-III Mean (SD) age: 67 (10) and 70 (8) N=96	• Postoperative pain within 30 days • Postoperative use of analgesia • Length of stay • Mobilisation within 24 hours after surgery	UK
Hofstad 2015[101]	All people had regional through spinal anaesthesia with bupivacaine. The LIA group had ropivacaine and epinephrine in saline injected into the soft tissue as 3 specific points during surgery. An LIA placebo with saline was used in the other group.	People scheduled for elective primary THA regardless of age, ASA score, or type of prosthesis. Mean (range) age: 65 (24-88) and 66 (49-85) N=116	No relevant outcomes extracted	Norway
Liu 2011[140]	All people had regional via spinal anaesthesia.	Adults under 80 years of age with osteoarthritis, ASA I–III,	• Thromboembolic complications within 90	China

Study	Details of interventions	Population	Outcomes	Comments
	The LIA group had morphine, bupivacaine, betamethasone, and epinephrine, mixed with saline. Injected into soft tissue three times during surgery. The non-LIA group was given LIA placebo using saline.	normal or low body mass index, scheduled total primary unilateral hip arthroplasty under standard spinal anaesthesia. Mean (SD) age: 79 (9) N=80	days • Nausea within 30 days	
Lunn 2011[143]	All people had regional via lumbar spinal anaesthesia with option of sedation with propofol. The LIA group had intraoperative LIA using ropivacaine.	Adults scheduled for elective unilateral primary total hip replacement. Mean (range) age: 67 (48-82) and 67 (35-87) ASA grade: I-III N=120	• Number of people with postoperative use of analgesia • Mobilisation within 24 hours after surgery	Denmark
Murphy 2012[165]	All people had regional via spinal anaesthesia using bupivacaine. The LIA group had levobupivacaine in saline that was injected in various locations intraoperatively. Placebo LIA was using saline was used the other group.	People undergoing primary hip arthroplasty for osteoarthritis ASA grade: not detailed Mean (SD) age: 54 (15) and 57 (11) N=91	• Postoperative use of analgesia	Republic of Ireland
Wylde 2015[236]	All people had regional via spinal anaesthesia using bupivacaine. The LIA group had intraoperative bupivacaine with adrenaline mixed in saline injected into the joint capsule and short external rotators, fascia, fat, and subcutaneous tissue before closure of the wound.	People undergoing primary unilateral THR for osteoarthritis ASA grade: not detailed Mean (SD) age: 66 (11) and 66 (10) N=322	• Postoperative pain: no pain on admission to recovery ward • Nausea within 30 days	UK

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Study	Details of interventions	Population	Outcomes	Comments
Regional anaesthesia with nerve block versus regional anaesthesia (RCTs)				
Goytizolo 2016[90]	All people had regional anaesthesia via combined spinal–epidural (CSE) anaesthesia. The nerve block received a lumbar plexus block.	People 60 to 100 years old with ASA score I-III who could safely undergo neuraxial anaesthesia and were scheduled for primary total hip arthroplasty. Mean (SD) age: 70 (8) and 70 (11) N=92	• Postoperative use of analgesia • Nausea within 30 days	Republic of Ireland
Green 2014[91]	All people had regional via spinal anaesthesia. The nerve block group received a psoas compartment block using bupivacaine.	People scheduled for primary total hip replacement. ASA: unclear Age: unclear N=53	• Postoperative pain within 30 days • Time to postoperative use of analgesia • Mobilisation within 24 hours after surgery	Republic of Ireland
Regional anaesthesia with LIA versus regional anaesthesia with nerve block (RCT)				
Kuchalik 2017[134]	All people had regional via spinal anaesthesia using bupivacaine. The LIA group had ropivacaine, ketorloac and adrenaline injected in 3 locations during surgery. The nerve block group had a femoral nerve block using ropivacaine.	Adults 80 years old or younger with ASA I-III and scheduled for hip arthroplasty. Mean (SD) age: 64 (7) and 63 (8) N=56	• Postoperative use of analgesia • Nausea within 30 days	Sweden
General anaesthesia with LIA versus general anaesthesia (RCTs)				
Chen 2010[40]	All people had general anaesthesia with propofol and fentanyl. The LIA group had a subcutaneous injection of	People with osteoarthritis or osteonecrosis, aged 18 to 80 years old, undergoing unilateral THA. Mean (SD) age: 52 (13) and	• Postoperative use of analgesia • Length of stay • Nausea within 30 days	Taiwan

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Study	Details of interventions	Population	Outcomes	Comments
	bupivacaine after closing of the capsule followed by regular bupivacaine.	54 (14) ASA status: I-III N=92		
Titman 2018[222]	All people had general anaesthesia via target controlled infusion (TCI) with propofol and remifentanil. The LIA group had a mixture of ropivacaine and saline through 3 injections into the periarticular tissues.	People with ASA I-III scheduled for elective cemented THA. Mean (SD) age: 76 (7) and 77 (6) N=40	• Postoperative neurocognitive decline within 30 days • Postoperative use of analgesia	Sweden
Villatte 2016[230]	All people had general anaesthesia with standardised protocol: a combination of hypnotic, opioid and curare. The LIA group had ropivicaine and epinephrine administered twice during surgery.	People 50 to 85 years old with degenerative hip disease or rheumatoid arthritis undergoing THA Mean age: 67 ASA grade: unclear N=150	• Postoperative pain within 30 days • Postoperative use of analgesia • Time to mobilisation	France
Zoric 2014[238]	All people had standardised general anaesthesia. Administration of anaesthetic drugs was left to the discretion of the attending physician. The LIA group had ropivacaine after putting in the implants. Those not in the LIA group were given a LIA placebo using saline.	People aged from 18 to 80 years old undergoing primary homolateral THA by postero-lateral incision under general anaesthesia. ASA grade: I-III Age range: 38-70 and 42-80 N=60	• Number of people using postoperative NSAIDs • Length of stay • Nausea within 30 days • Mobilisation within 24 hours after surgery	France
General anaesthesia with nerve block versus general anaesthesia (RCTs)				
Kratz 2015[132]	All people had general anaesthesia. The nerve block group had a supplemental femoral nerve block.	People undergoing hip arthroplasty ASA grade I or II Mean (SD) age: 67 (12) and 66 (14)	• Postoperative pain within 30 days • Postoperative use of analgesia	Germany

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Study	Details of interventions	Population	Outcomes	Comments
		N=80		
Nicholson 2002[171]	All people had general anaesthesia induced with fentanyl and propofol or etomidate. The Nerve block group received a three-in-one nerve block (femoral nerve, lateral cutaneous nerve of thigh and obturator nerve) performed using lidocaine and bupivacaine.	Women aged over 55 years who had been amenorrhoeic for at least 2 years undergoing primary total hip replacement. Mean (SD) age: 76 (8) and 75 (8) and 78 (8) ASA grade: not detailed N=36	No relevant outcomes extracted	UK
Twyman 1990[224]	All people had normotensive general anaesthesia. The Nerve block group received a lumbar plexus block.	Women with osteoarthritis undergoing cemented primary total hip replacement ASA grade: not detailed Age: not detailed N=20	No relevant outcomes extracted	UK
General anaesthesia with LIA versus general anaesthesia with nerve block (RCT)				
Fahs 2018[69]	All people had general endotracheal anaesthesia (without neuraxial blockade). The LIA group had periarticular anaesthetic soft-tissue infiltration used ropivacaine, epinephrine, morphine, and ketorolac diluted in saline injected after component implantation and before closure, into the tissues surrounding the hip joint. The nerve block group received a psoas compartment block used ropivacaine in saline.	People with primary osteoarthritis, undergoing unilateral primary THA via DAA by the senior surgeon. Mean (SD) ASA score: 2.4 (0.5) and 2.2 (0.5) Mean (SD) age: 68 (8) and 65 (8) N=100	• Quality of life within 30 days • Postoperative use of analgesia • Length of stay	USA

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Study	Details of interventions	Population	Outcomes	Comments
Regional anaesthesia versus general anaesthesia				
RCTs				
Eroglu 2005[66]	The regional group had hypotensive epidural anaesthesia (HEA). A combination of an extensive epidural block and an intravenous (IV) infusion of low-dose epinephrine. The general anaesthesia group had hypotensive total IV anaesthesia (HTIVA). Anaesthesia was induced with propofol and maintained with propofol and remifentanil.	People 50 - 80 years old and ASA I-III who were scheduled for primary unilateral total hip replacement. Mean (SD) age: 64 (13) and 62 (10) N=40	No relevant outcomes extracted	Turkey
Gottschalk 2014[89]	The regional group had lumbar spinal anaesthesia with bupivacaine. The general anaesthesia group was induced using sufentanil and propofol and maintained with sevoflurane.	People aged 18-75 years old with ASA physical status I - III undergoing elective total hip replacement The trial was stratified into those people with diabetes and those without diabetes. The results presented separately for each group. Mean (SD) age: 74 (6) and 71 (10) and 70 (8) and 73 (7) N=98	• Postoperative use of analgesia	Germany
Harsten 2015[96]	The regional group had spinal anaesthesia using bupivacaine. The general anaesthesia group had anaesthesia with remifentanil and propofol.	People 45-85 years old and ASA I-III with osteoarthritis scheduled for THA. Mean (SD) age: 68 (9), 66 (8) N=120	• Length of stay • Mobilisation within 24 hours after surgery	Sweden
Hogevold 2000[102]	The regional group had	People ASA I-II undergoing	No relevant outcomes	Norway

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Study	Details of interventions	Population	Outcomes	Comments
	spinal/epidural anaesthesia using bipuvicaine. The general anaesthesia group were induced by IV thiopental, pancuronium, and fentanyl.	uncemented primary hip arthroplasty ASA grade I or II Mean age: 53 N=12	extracted	
Modig 1987[162]	The regional group had continuous lumbar epidural anaesthesia using bupivicaine and epinephrine. The general anaesthesia groups had either inhalational general anaesthesia or intermittent positive pressure ventilation (IPPV). Both induced by IV thiopentone after IV atropine.	People with advanced osteoarthritis of the hip and ASA I or II who are scheduled to undergo total hip replacement. Mean (SD) age: 67 (7) and 68 (8) and 65 (8) N=38	No relevant outcomes extracted	Sweden
Observational studies				
Basques 2015[18]	Regional anaesthesia was always spinal anaesthesia. No details of the medications use for regional or general anaesthesia. Intervention groups were propensity score matched to control for selection bias between the spinal and general anaesthesia.	People who had primary elective total hip arthroplasty for osteoarthritis N=20936	Mortality within 90 days Propensity-adjusted multivariate logistic regression used to analyse the data.	USA American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database from 2010 to 2012.
Donauer 2018[62]	No details of the medications use for regional or general anaesthesia.	People who had hip replacement surgery under ICD-9 code: 81.54 Mean (SD) age: 63 (13) and 63 (11) N=1713	No outcomes extracted	Europe, Israel, and USA Analysis of people in the International PAIN OUT Registry. This takes data from institutions.

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Study	Details of interventions	Population	Outcomes	Comments
Haughom 2015[97]	Regional anaesthesia was either spinal or epidural. No details of the medications use for regional or general anaesthesia.	People who had primary total hip arthroplasty. Mean age: 66 and 64 N=28857	No outcomes extracted	USA National Surgical Quality Improvement Database (NSQIP). It gathered data from 400 hospitals in 2012. This dataset was from 2005 to 2012.
Hunt 2013[105]	Regional anaesthesia as always spinal anaesthesia. No details of the medications use for regional or general anaesthesia.	People who had primary total hip replacement surgery N=262240 (in the two intervention groups of interest)	Mortality within 90 days Cox proportional hazards model utilised to analyse the data	UK Data taken from National Joint Registry for England and Wales from April 2003 to December 2011. The NHS Personal Demographics Service provided dates of death from the Office for National Statistics.
Maurer 2007[151]	Regional anaesthesia as always spinal anaesthesia normally using bupivavaine. Propofol used to induce general anaesthesia.	People who underwent primary unilateral total hip replacement Mean (SD) age: 55 (16) and 63 (14) N=606	No outcomes extracted	USA Data from surgery at Hospital for Joint Diseases in New York, USA from January 1995 to January 1998
General and regional anaesthesia versus general anaesthesia with nerve block (RCT)				
Duarte 2009[64]	All people had general anaesthesia using alfentanil, propofol, and succinylcholine. The regional anaesthesia group had continuous epidural lumbar block using ropivacaine. The nerve block group received posterior lumbar plexus nerve block using ropivacaine.	Consecutive people (ASA I to III) scheduled for THA Mean (SD) age: 61 (15) and 58 (16) N=41	No relevant outcomes extracted	Brazil

See Appendix D: for full evidence tables.

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1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: RCT evidence summary: regional anaesthesia with nerve block versus regional anaesthesia

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Regional anaesthesia with nerve block versus regional anaesthesia (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain within 30 days numerical rating scale. Scale from: 0 to 10.	53 (1 study) 2 hours after surgery	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean postoperative pain within 30 days in the control groups was 1.23	The mean postoperative pain within 30 days in the intervention groups was 1.08 lower (1.9 to 0.26 lower)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Postoperative use of analgesia	92 (1 study) during hospital stay	⨁⨁⨁⊖ MODERATE[2] due to imprecision		The mean postoperative use of analgesia in the control groups was 71 mg	The mean postoperative use of analgesia in the intervention groups was 11 lower (25.33 lower to 3.33 higher)
Time to postoperative use of analgesia	53 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean time to postoperative use of analgesia in the control groups was 261 minutes	The mean time to postoperative use of analgesia in the intervention groups was 63.27 higher (24.82 lower to 151.36 higher)
Nausea within 30 days	90 (1 study) 1 days	⨁⨁⊖⊖ LOW[2] due to imprecision	RR 1.22 (0.62 to 2.39)	250 per 1000	55 more per 1000 (from 95 fewer to 348 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Regional anaesthesia with nerve block versus regional anaesthesia (95% CI)
Mobilisation within 24 hours after surgery	53 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.95 (0.77 to 1.18)	889 per 1000	44 fewer per 1000 (from 204 fewer to 160 more)

[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.

Table 4: RCT evidence summary: Regional anaesthesia with LIA versus regional anaesthesia with nerve block

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Regional anaesthesia with LIA versus regional anaesthesia with nerve block (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain	Not reported				
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Postoperative use of analgesia	56 (1 study) 0-24 hours after surgery	⨁⨁⨁⊖ MODERATE[1] due to imprecision		The mean postoperative use of analgesia in the control groups was 30 mg	The mean postoperative use of analgesia in the intervention groups was 13.6 lower (20.97 to 6.23 lower)
Nausea within 30 days	56 (1 study) 4-24 hours	⨁⨁⊖⊖ LOW[1] due to	RR 0.74 (0.43 to	556 per 1000	144 fewer per 1000 (from 317 fewer to 161 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Regional anaesthesia with LIA versus regional anaesthesia with nerve block (95% CI)
	after surgery	imprecision	1.29)		

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 5: RCT evidence summary: Regional anaesthesia with LIA versus regional anaesthesia

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Regional anaesthesia with LIA versus regional anaesthesia (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain within 30 days Visual Analogue Scale. Scale from: 0 to 10.	92 (1 study) 19-24 hours after surgery	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean postoperative pain within 30 days in the control groups was 0.98	The mean postoperative pain within 30 days in the intervention groups was 0.3 lower (0.66 lower to 0.06 higher)
Postoperative pain no pain on admission to recovery ward	322 (1 study)	⨁⨁⨁⨁ HIGH	RR 1.01 (0.88 to 1.17)	698 per 1000	7 more per 1000 (from 84 fewer to 119 more)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications within 90 days	78 (1 study) 6-12 months	⨁⨁⊖⊖ LOW[2] due to imprecision	RR 0.86 (0.32 to 2.32)	179 per 1000	25 fewer per 1000 (from 122 fewer to 237 more)
Hospital readmission	Not reported				
Postoperative use of analgesia	183	⨁⊖⊖⊖		The mean postoperative use	The mean postoperative use of

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Regional anaesthesia with LIA versus regional anaesthesia (95% CI)
mg. Scale from: 0 to 1.	(2 studies) 3.5 days	VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision		of analgesia in the control groups was 17.5 mg	analgesia in the intervention groups was 0.55 standard deviations lower (1.31 lower to 0.21 higher)
Number of people with postoperative use of analgesia	201 (3 studies) at varying in-hospital time points	⨁⨁⊖⊖ LOW[2] due to imprecision	RR 0.63 (0.31 to 1.27)	185 per 1000	68 fewer per 1000 (from 127 fewer to 50 more)
Length of stay	92 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean length of stay in the control groups was 3.9 days	The mean length of stay in the intervention groups was 0.4 lower (1.31 lower to 0.51 higher)
Nausea within 30 days	487 (4 studies) unclear	⨁⨁⨁⊖ MODERATE[2] due to imprecision	RR 0.85 (0.69 to 1.03)	449 per 1000	67 fewer per 1000 (from 139 fewer to 13 more)
Mobilisation on day 1 after surgery	92 (1 study)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 1.02 (0.88 to 1.19)	870 per 1000	17 more per 1000 (from 104 fewer to 165 more)
Mobilisation 8 hours after surgery	120 (1 study)	⨁⊖⊖⊖ VERY LOW[2,4] due to indirectness, imprecision	RR 1.57 (0.65 to 3.78)	117 per 1000	67 more per 1000 (from 41 fewer to 324 more)

[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.

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Regional anaesthesia with LIA versus regional anaesthesia (95% CI)

[3] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.
[4] Outcome is 8 hours after surgery rather than 1 day

Table 6: RCT evidence summary: regional anaesthesia 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 Regional anaesthesia (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain	Not reported				
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Postoperative use of analgesia	68 (2 studies) unclear	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean postoperative use of analgesia in the control groups was 3.3 mg	The mean postoperative use of analgesia in the intervention groups was 2.89 lower (4.27 to 1.51 lower)
Length of stay	118 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean length of stay in the control groups was 26 hours	The mean length of stay in the intervention groups was 4 hours higher (1.33 to 6.67 higher)
Mobilisation within 24 hours after surgery	118 (1 study) 12 hours	⨁⨁⨁⊖ MODERATE[1] due to risk of	RR 0.98 (0.94 to	1000 per 1000	20 fewer per 1000 (from 60 fewer to 30 more)

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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 Regional anaesthesia (95% CI)
	after surgery	bias	1.03)		
Mortality within 30 days of surgery	20936 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[2] due to imprecision	OR 1.19 (0.57 to 2.53)	1344 per 1000000	255 more per 1,000,000 (from 578 fewer to 2049 more)

[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.

Table 7: Observational studies evidence summary: regional anaesthesia versus general anaesthesia

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Adjustment for confounding factors
Mortality within 90 days of surgery	262,240 (1 study)	VERY LOW[1] due to imprecision	Adjusted HR 0.85 (0.74 to 0.97)	Multivariate analysis using age and gender, mechanical and chemical thromboprophylaxis, and year of operation, approach, comorbidity, body-mass index, ethnic origin, and social deprivation area.
Comparison below is general anaesthesia versus regional anaesthesia as reported in the study				
Mortality within 30 days of surgery	20,936 (1 study)	VERY LOW[1] due to imprecision	Adjusted OR 1.19 (0.57 to 2.53)	Propensity-adjusted multivariate logistic regression. Multivariate regression adjusted for baseline differences in patient demographic characteristics and comorbidities as well as the propensity score.

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 8: RCT evidence summary: General anaesthesia with LIA versus general anaesthesia with nerve block

Outcomes	No of	Quality of	Relativ	Anticipated absolute effects

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	Participants (studies) Follow up	the evidence (GRADE)	e effect (95% CI)	Risk with Control	Risk difference with General anaesthesia with LIA versus general anaesthesia with nerve block (95% CI)
Mortality	Not reported				
Quality of life within 30 days via Quality of Recovery QoR-40. Scale from: 40 to 200.	99 (1 study) 1 days	⊕⊕⊕⊖ MODERATE [1] due to imprecision		The mean quality of life within 30 days via quality of recovery in the control groups was 177	The mean quality of life within 30 days via quality of recovery in the intervention groups was 5.9 higher (1.05 to 10.75 higher)
Postoperative pain	Not reported				
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Postoperative use of analgesia	99 (1 study) 1 days	⊕⊕⊕⊕ HIGH		The mean postoperative use of analgesia in the control groups was 46.2 mg	The mean postoperative use of analgesia in the intervention groups was 3.2 lower (15.42 lower to 9.02 higher)
Length of stay	99 (1 study)	⊕⊕⊕⊕ HIGH		The mean length of stay in the control groups was 1.4 days	The mean length of stay in the intervention groups was 0 higher (0.28 lower to 0.28 higher)

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 9: RCT evidence summary: General anaesthesia with LIA versus general anaesthesia

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with General anaesthesia with LIA versus general anaesthesia (95% CI)
Mortality	Not reported				
Quality of life	Not reported				

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with General anaesthesia with LIA versus general anaesthesia (95% CI)
Postoperative pain within 30 days Visual Analogue Scale. Scale from: 0 to 10.	150 (1 study) 4 hours after surgery	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean postoperative pain within 30 days in the control groups was 2.87	The mean postoperative pain within 30 days in the intervention groups was 0.48 lower (0.97 lower to 0.01 higher)
Postoperative neurocognitive decline within 30 days	35 (1 study) 10 days	⨁⊖⊖⊖ VERY LOW[1,5] due to risk of bias, imprecision	RD 0 (-0.11 to 0.11)[4]	0 per 1000	0 fewer per 1000 (from 110 fewer to 110 more)[3]
Postoperative use of analgesia varying methods	276 (3 studies) 2 days	⨁⨁⨁⊖ MODERATE[1] due to risk of bias		The mean postoperative use of analgesia in the control groups was 24 mg	The mean postoperative use of analgesia in the intervention groups was 1.94 lower (6.2 lower to 2.33 higher)
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Number of people using postoperative NSAIDs	58 (1 study) while admitted in hospital	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1 (0.28 to 3.62)	138 per 1000	0 fewer per 1000 (from 99 fewer to 361 more)
Length of stay	241 (2 studies)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias		The mean length of stay in the control groups was 6.15 days	The mean length of stay in the intervention groups was 0.1 lower (0.4 lower to 0.2 higher)
Nausea within 30 days days	149 (2 studies) 4 days	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias,	RR 0.82 (0.51 to 1.32)	347 per 1000	62 fewer per 1000 (from 170 fewer to 111 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with General anaesthesia with LIA versus general anaesthesia (95% CI)
		imprecision			
Mobilisation within 24 hours after surgery	58 (1 study)	⨁⊖⊖⊖ VERY LOW[1,6] due to risk of bias, indirectness	RR 1 (0.22 to 4.55)	103 per 1000	0 fewer per 1000 (from 81 fewer to 367 more)
Time to mobilisation	150 (1 study)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias		The mean time to mobilisation in the control groups was 1.9 days	The mean time to mobilisation in the intervention groups was 0.1 lower (0.4 lower to 0.2 higher)

[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
[4] Comparative effect analysed using risk difference due to zero events in both treatment arms
[5] Downgraded one increment for imprecision as it is a small study with no events.
[6] Study outcome was walk in the corridor on postoperative day 2

Table 10: RCT evidence summary: General anaesthesia with 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 Control	Risk difference with General anaesthesia with nerve block versus general anaesthesia (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain within 30 days Visual Analogue Scale. Scale from: 0 to 10.	52 (1 study) 1 days	⨁⨁⊖⊖ LOW[1] due to risk of bias		The mean postoperative pain within 30 days in the control groups was 4	The mean postoperative pain within 30 days in the intervention groups was 2.3 lower (3.42 to 1.18 lower)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with General anaesthesia with nerve block versus general anaesthesia (95% CI)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Postoperative use of analgesia	52 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean postoperative use of analgesia in the control groups was 292 mg	The mean postoperative use of analgesia in the intervention groups was 223 lower (426.43 to 19.57 lower)

[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.

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1.5 Economic evidence

1.5.1 Included studies

Two health economic studies were identified with the relevant comparison and have been included in this review. [88, 147]. The studies are summarised in the health economic evidence profile below (Table 11) and the health economic evidence table in Appendix H: One original threshold analysis was conducted which can be found in Appendix I:

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

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

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1.5.3 Summary of studies included in the economic evidence review

Table 11: Health economic evidence profile: LAI in addition to a standard anaesthetic regimen versus standard anaesthetic regimen only

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Marques 2015[147] [UK]	Directly applicable[(a)]	Minor limitations[(b)]	A within-trial cost-utility analysis comparing a 1) standard anaesthetic regimen[(c)] to 2) a LAI in addition to a standard anaesthetic regimen. The population was people who underwent a primary THR with a 12 month time horizon.	LAI in addition to a standard anaesthetic regimen saved £86 per person.	LAI in addition to a standard anaesthetic regimen gave 0.052 more QALYS per person.	LAI in addition to a standard anaesthetic regimen dominates (is less costly and more effective) standard anaesthetic alone.	A series of one way deterministic sensitivity analyses (cost of medication, inpatient stays and anomalous patients) were conducted. The dominance of the intervention was robust to all scenarios. LAI was cost effective at a threshold of £20,000 per QALY gained in over 98% of simulations.

Abbreviations: LAI; local anaesthetic wound infiltration; QALY= quality-adjusted life years; RCT= randomised controlled trial; THR: total hip replacement;

(a) A within-trial cost-utility analysis with relevant comparators. QALYs are used as the outcome and derived using EQ-5D.

(b) Complete cost and QALY data was available for only 159/322 (49%) of participants. The final dataset therefore included imputed missing costs and outcome data. Outcomes are from a single RCT rather than a systematic review.

(c) The standard anaesthetic regimen consisted of spinal anaesthesia alone or in combination with sedation/light general anaesthesia.

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Table 12: Health economic evidence profile: Spinal anaesthesia versus general anaesthesia

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Gonano 2006 [88] [Austria]	Partially applicable[(a)]	Potentially serious limitations[(b)]	A cost comparison of individuals who have undergone a THR and taking part in an RCT comparing spinal anaesthesia to general anaesthesia. Time horizon is restricted to inpatient time.	Spinal anaesthesia saves £29.18 per patient	N/A	Spinal anaesthesia is cost saving compared to general anaesthesia	Four scenario analyses were conducted. These explored varying the use of muscle relaxants, fresh gas flow, and use of isoflurane instead of sevoflurane. Spinal anaesthesia being cost saving was robust to all these analyses.

Abbreviations: RCT= randomised controlled trial; THR: Total hip replacement; TKR: Total knee replacement.

(a) A cost comparison study which does not include all relevant costs.

(b) No health outcomes are used to conduct a cost effectiveness analysis. Personnel costs are not included. The overall study population included both TKR and THR procedures but the results presented are from the THR sub-group, so the sample size is small. The time horizon only covers part of the inpatient time period.

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1.5.4 Health economic modelling

A threshold analysis was conducted on the addition of nerve blocks to an anaesthetic regimen. 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

The unit costs presented in Table 13 are for general and regional anaesthesia in a hip fracture population. Hip fracture is outside of the scope for this guideline. However, the committee felt the costs would be informative for a primary elective hip arthroplasty population. Table 14 shows the UK cost for the addition of a nerve block to any anaesthetic regimen when varying the time it takes to administer a nerve block and if the cost of theatre time is included or not.

Table 13: Mean costs of anaesthesia for hip fracture in a UK hospital in 2010

Type of anaesthesia	Anaesthesia equipment (SD)	Airway equipment (SD)	Personnel (SD)	Drugs (SD)	Gases/inhalation agents (SD)	Total (SD)_
Spinal	£ 66.73 (30.05)	£1.81 (0)	£105.90 (0)	£19.03 (11.00)	£0.43 (0.13)	£193.81 (37.49)*
General	£108.15 (38.53)	£25.68 (2.28)	£106.76 (0)	£25.17 (11.04)	£6.26 (3.94)	£270.58 (44.68)*

Source: Chakladar2010[38]

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

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	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)[47]; CG124[168]

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

(b) It was assumed that the cost of theatre time from CG124[168] did not include personnel costs

(c) NHS Hospital is Peterborough and Stamford Hospitals NHS Foundation Trust which provided information for CG124[168]

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1.6 Evidence statements

1.6.1 Clinical evidence statements

24 RCTs covering 8 comparisons were included in the evidence review with relevant outcomes found for 7 of the comparisons. Data from 2 observational studies was utilised for the mortality within 90 days outcome for the regional anaesthesia versus general anaesthesia comparison.

Regional anaesthesia with nerve block versus regional anaesthesia was compared in 2 RCTs (n=145) with the majority of outcomes graded very low quality. A benefit was found for regional anaesthesia with nerve block in postoperative pain. No difference between treatment groups was found for 2 postoperative use of analgesia outcomes, nausea, or mobilisation. No outcomes favoured regional anaesthesia alone.

Regional anaesthesia with LIA versus regional anaesthesia with nerve block was compared in 1 RCT (n=56). All outcomes favoured regional anaesthesia with LIA. These were postoperative use of analgesia (moderate quality) and nausea (low quality).

Regional anaesthesia with LIA versus regional anaesthesia was compared in 7 RCTs (n=900) with quality ranging from high to very low. A benefit was found for regional anaesthesia with LIA in 2 postoperative use of analgesia outcomes, and 1 mobilisation outcome. All other outcomes indicated no difference between treatment groups, these were 2 postoperative pain outcomes, thromboembolic complications, length of stay, nausea, and 1 mobilisation outcome.

Regional anaesthesia versus general anaesthesia was compared in 5 RCTs (n=308) and 5 observational studies (n=314,352). The RCT evidence indicated a benefit of regional anaesthesia in postoperative use of analgesia (very low quality) and conversely a benefit was found for general anaesthesia in terms of length of stay (very low quality). No difference between interventions for mobilisation (moderate quality). 2 observational studies did not find a clinically important difference between treatment groups in terms of mortality (n=283,176, very low quality).

General anaesthesia with LIA versus general anaesthesia with nerve block was compared in 1 RCT (n=100) with outcomes graded as moderate or high quality. A benefit was found for general anaesthesia with LIA in terms of quality of life. No difference between treatment groups was found for postoperative use of analgesia and length of stay. No outcomes favoured general anaesthesia with nerve block.

General anaesthesia with LIA versus general anaesthesia was compared in 4 RCTs (n=342). All 8 outcomes indicated no difference between interventions. These were postoperative pain (very low quality), postoperative neurocognitive decline (very low quality), postoperative use of analgesia (moderate quality), length of stay (moderate quality), nausea (very low quality), and 2 mobilisation outcomes (moderate or very low quality).

General anaesthesia with nerve block versus general anaesthesia was compared in 3 RCTs (n=136). 1 RCT contained 2 relevant outcomes and both found a benefit for general anaesthesia with nerve block. These 2 outcomes were postoperative pain (low quality) and postoperative use of analgesia (very low quality).

1.6.2 Health economic evidence statements

One cost utility analysis found that using local anaesthetic wound infiltration in addition to a regional and/or general anaesthesia was dominant (less costly and more effective) compared to regional and/or general anaesthesia alone in people having an elective total hip replacement. This analysis was assessed as directly applicable with minor limitations.

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One cost comparison found that using spinal anaesthesia was cost saving compared to general anaesthesia in people having an elective total hip replacement. This analysis was assessed as partially applicable with potentially serious limitations.

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, and hospital readmission. The follow-up time point for mortality, the most critical outcome, was specified to be 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 utilised 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 balance these factors between treatment groups. Postoperative pain is of critical importance as it represents a central aspect of a person's initial experience of 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 reduces future chronic pain. Postoperative neurocognitive decline is a key decision making outcome for the people undergoing joint replacement surgery. The committee anaesthetist said that neurocognitive decline was a major concern highlighted by people when these decision making conversations occur.

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 a very important outcome to those undergoing surgery and has economic implications. The anaesthetic approach may impact when a person can mobilise themselves. A person's ability mobilise themselves shortly after surgery represents the early experience of a hip joint replacement and also whether they can be discharged from hospital.

1.7.1.2 The quality of the evidence

The overall outcome quality ranged from high to very low. More outcomes were assessed as low or very low quality than moderate or high quality.

The evidence was often downgraded for risk of bias because studies that did not state an adequate method of randomisation or gave an adequate description of allocation concealment. A further reason for risk of bias was due to the difficulty of blinding in surgical treatment meant that subjective outcomes were occasionally assessed by people who knew the anaesthetic treatment used.

Two thirds of the outcomes were downgraded in quality due to imprecision. Only 1 outcome was downgraded for inconsistency. This was not explained by subgroup analysis and a random effects model was utilised.

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1.7.1.3 Benefits and harms

24 randomised controlled trials were included in the evidence review. These trials encompassed 8 comparisons though relevant evidence was found for 7 of the comparisons. The study investigating the 8th comparison did not contain relevant outcomes. A network meta-analysis was considered for this analysis but there were no suitable outcomes reported across the comparisons to facilitate this approach. Many studies were excluded as it was unclear if the hip arthroplasty being undertaken was primary arthroplasty. The committee agreed that revision surgery is different enough from primary arthroplasty that studies where primary arthroplasty was not specified should be excluded. In addition it was important that the postoperative analgesia followed the same protocol for both treatment groups in each study to prevent confounding.

Comparisons including only regional anaesthesia

Regional anaesthesia alone was compared to regional anaesthesia with LIA and regional anaesthesia with nerve block. Regional anaesthesia alone often appeared to be of similar effectiveness to regional anaesthesia augmented with LIA or nerve blocks. 9 outcomes indicated no difference between the two anaesthetic regimes. However 4 outcomes did favour augmented regional over regional alone though conversely 1 outcome indicated a benefit of regional alone over augmented regional. When regional with LIA was compared to regional with nerve block, the only 2 outcomes indicated a benefit of the former. However these outcomes came from 1 study with 56 participants.

Comparisons including only general anaesthesia

General anaesthesia alone was compared to general anaesthesia with LIA and all 9 outcomes indicated no difference between the approaches. General anaesthesia alone was compared to general anaesthesia with nerve block in 2 outcomes taken from 1 study with 80 participants, and both indicated a benefit of general with nerve block. General with LIA was compared to general with nerve block in 3 outcomes taken from 1 study with 100 participants. These indicated a benefit for general with LIA for quality life and no difference for the other 2 outcomes.

Comparisons including both regional and general anaesthesia

2 studies with extractable outcomes compared general to regional anaesthesia. The studies found a benefit for regional in postoperative use of analgesia, a benefit for general in mobilization within 24 hours, and no difference in length of stay. The RCT clinical evidence data did not provide strong enough evidence to differentiate between regional or general anaesthesia.

It was then decided to look for mortality outcomes in non-randomised studies comparing regional anaesthesia to general anaesthesia. The committee were interested in this particular comparison because it is thought that general anaesthesia leads to greater mortality than regional anaesthesia and this might be a method by which they could be separated. This data was sought because the RCTs were of insufficient size to accurately assess an outcome as rare as mortality. NJR data was utilised in one study where it was adjusted for confounding factors. 5 relevant non-randomised studies were found but only two reported mortality. Both studies consistently reported a small benefit for regional anaesthesia over general anaesthesia though one study did have very wide confidence intervals. However despite the studies showing a small benefit of regional anaesthesia, the rarity of mortality in this surgery did not indicate a clinically important effect and the committee did not decide to recommend regional anaesthesia over general anaesthesia.

When discussing the overall arc of the evidence the committee discussed when regional anaesthesia alone was compared to regional anaesthesia augmented with LIA or nerve

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blocks and when general anaesthesia alone was compared to general anaesthesia augmented with LIA or nerve blocks. There was commonly outcomes that indicated no difference between treatments but outside of that there was a benefit of the augmented anaesthesia. The solo interventions rarely show a clinically important benefit.

The committee agreed that overall there was no evidence found for postoperative neurocognitive decline for any of the approaches and this is an important benefit for the person undergoing surgery. The evidence found did not indicate any differences in length of stay and in nearly every case in terms of mobilisation.

The committee agreed that the evidence did not indicate a difference between general or regional anaesthesia. In addition there did appear to be some benefit of augmenting these approaches with LIA or nerve blocks. The guideline anaesthetist indicated that it makes sense to utilise additional techniques on top of regional or general because multimodal anaesthesia approaches the complex problem from multiple angles and provides more ways of reducing postoperative pain.

The committee made recommendations for offering regional or general anaesthesia in combination with LIA, or nerve blocks as an alternative to LIA, based on their experience and the evidence. They agreed the combination reduces postoperative pain and the evidence showed that both nerve blocks and LIA are beneficial when used with general or regional anaesthesia.

The committee were keen to highlight the personalised care aspect that should stay within the anaesthetist's sphere of control. The knowledge and experience of the anaesthetist should be utilised when considering patient characteristics in accordance with best practice. Thus all options can be considered by the anaesthetist given individual patient circumstances/characteristics.

A patient member of committee indicated that people get confused around anaesthesia choices and full explanations of the risks and benefits of each approach are important person's wellbeing both before and after surgery. These explanations must be pitched correctly for a benefit to be seen.

1.7.2 Cost effectiveness and resource use

Two studies were presented; the first found that the addition of LIA to regional or general was dominant (less costly and more effective) compared to regional or general alone. The second found that regional (spinal) anaesthesia was cost saving over general anaesthesia. There was a lack of economic evidence presented regarding the use of nerve blocks.

Any difference in mortality and morbidity was not fully accounted for in the initial clinical review as the time horizon for inclusion was too short. The observational evidence subsequently presented suggested that there was not a significant difference in mortality between regional and general anaesthesia.

Unit costs of regional and general anaesthesia for a hip fracture population were presented. These showed that regional anaesthesia was cost saving. There was suggestion that these were representative of costs for a primary total hip replacement as well. However, there were also differing views put forward on if there was a true difference in costs. There was consensus that time is gained at the end of a total hip replacement using spinal anaesthesia as the patient leaves the theatre straight away. By contrast, for general anaesthesia the patient leaving the theatre must be timed with certain factors such as the different dressings applied. The lay perspective also discussed about personal experience of longer recovery times whilst under general anaesthetic. The cost of the extra recovery time represents an additional cost, however general may still be more appropriate for certain people.

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The committee discussed that there is a difference in analgesic time between LIA and nerve blocks. There was consensus that using LIA is unlikely to represent significant additional costs in terms of time or personnel as it is often administered in redundant theatre time.

A nerve block may take up to 5 minutes of additional theatre time 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 unit cost of £14.22 per minute for theatre time (including implant cost, personnel, overheads, consumables and facilities) presented from the economic evidence was thought to be very low; a more realistic unit cost of theatre time would be around £20.50 as included in CG124[168].

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 third factor, 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 8 hours on average for hip replacements. However, a 24 hour time horizon may be the most appropriate

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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).

The committee agreed that there is clinical benefit to the addition of nerve blocks, although they are only likely to be cost effective when administered by an experienced anaesthetist, theatre time is not included (so two anaesthetists are present) and the effect duration is longer. The circumstances when nerve blocks are cost effective may be found in some hospitals but not in others.

Due to evidence suggesting that the addition of LIA to regional or general anaesthesia is clinically and cost effective, a recommendation was made offering this combination of anaesthesia. As the committee thought there may be a clinical benefit when adding a nerve block to regional or general anaesthesia, but concerns remained regarding the cost effectiveness, a weaker recommendation was made to consider the use of a nerve block over LIA. As no clinical evidence was found for the addition of a nerve block to LIA and regional or general anaesthesia, no recommendation was made for this combination. There were roughly 75,000 total hip replacements in 2017, all of which require some form of anaesthetic. All orthopaedic units currently offer a choice of general or regional anaesthesia. Most will augment this with either LIA or a nerve block. Although the cost of nerve blocks varies, it is not expected that services currently offering LIA will change to nerve blocks. This recommendation is unlikely to lead to significant change from current practice.

1.7.3 Other factors the committee took into account

A committee member spoke about the NHS history vis-a-vis regional anaesthesia. In 1946 in the Chesterfield Royal Infirmary spinal anaesthetic was used in 3 people who were paralysed as a result. It was found that this was because the local anaesthetic used was contaminated but this led to a move away from regional anaesthesia and the legacy of this catastrophe is ongoing today.

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Appendices

Appendix A: Review protocols

Table 15: Review protocol: anaesthesia for hip joint replacement surgery

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Anaesthesia in hip joint replacement surgery
2.	Review question	In adults having primary elective hip joint replacement, what is the clinical and cost effectiveness of intraoperative anaesthetic approaches: regional anaesthesia or general anaesthesia, with or without nerve blocks and local infiltration analgesia, compared with each other or in combination?
3.	Objective	This review seeks to assess the most effective anaesthetic approach 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 hip joint replacement surgery

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ID	Field	Content
	being studied	
6.	Population	Inclusion: Adults having primary elective hip 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 nerve block General anaesthesia with local infiltration analgesia (during or after procedure) General anaesthesia with nerve block and local infiltration analgesia (during or after procedure) Regional anaesthesia Regional anaesthesia with nerve block Regional anaesthesia with local infiltration analgesia (during or after surgery) Regional anaesthesia with nerve block and local infiltration analgesia (during or after surgery)
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)

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ID	Field	Content
		Postoperative neurocognitive decline up to 30 days (dichotomous) Thromboembolic complications up to 90 days (VTE; dichotomous) Hospital readmission up to 30 days (dichotomous)
13.	Secondary outcomes (important outcomes)	Postoperative use of analgesia (dichotomous) Length of stay (continuous) Nausea up to 30 days (dichotomous) Mobilisation 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% confidence intervals will be calculated for each outcome.

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ID	Field	Content	
		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	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	

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ID	Field	Content		
21.	Anticipated or actual start date	02/02/19		
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] Agnès Cuyàs [Information specialist] Eleanor Priestnall [Project Manager]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		

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

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Table 16: 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).[167] **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,

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	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.

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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.[167]

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 17: 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.

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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.

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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

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	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

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	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

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	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 18: 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.

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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/

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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

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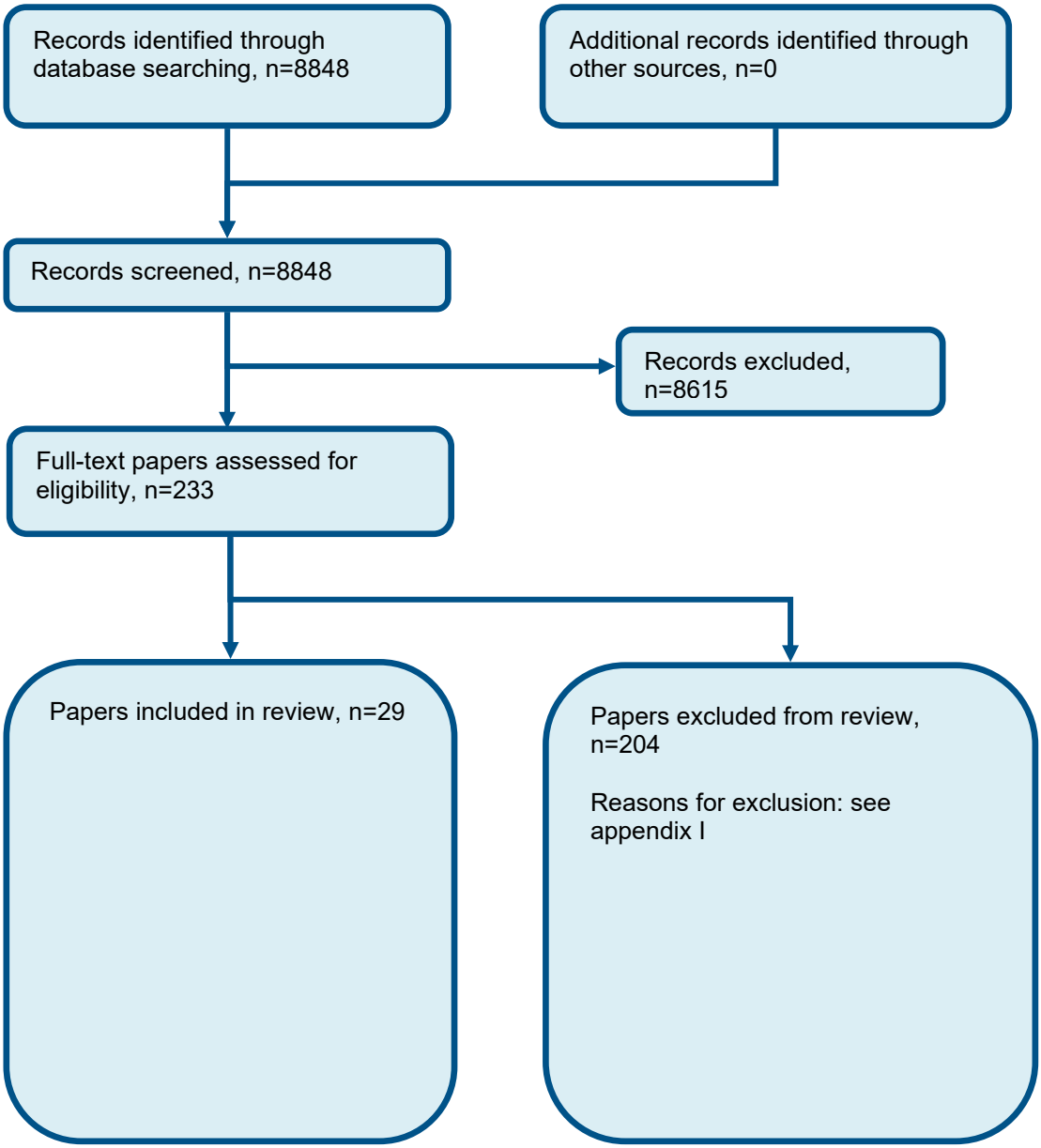
Appendix C: Clinical evidence selection

figure 1: Flow chart of clinical study selection for the review of anaesthesia for hip replacement surgery



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Appendix D: Clinical evidence tables

Study	APEX trial: Wylde 2015[236]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=322)
Countries and setting	Conducted in United Kingdom; Setting: UK elective orthopaedic centre
Line of therapy	Not applicable[1]
Duration of study	Intervention + follow up: Surgery and 12 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary unilateral THR for osteoarthritis
Exclusion criteria	Medical comorbidity that precluded spinal anaesthesia, regional blocks, or strong analgesics postoperatively because inability to tolerate these pain relief strategies may have influenced the trial results; severe dementia or psychiatric illness; listing for simultaneous bilateral joint replacement; previous participation in the trial; inability to understand English.

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

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Recruitment/selection of patients	People were recruited at the preoperative assessment clinic by a research nurse and randomized before surgery by the trial administrator.
Age, gender and ethnicity	Age - Mean (SD): 66 (11) and 66 (10). Gender (M:F): 133/189. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=163) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthetic using bupivacaine. Intraoperative local anaesthetic infiltration using bupivacaine with adrenaline. The local anaesthetic mixture was injected into the joint capsule and short external rotators, fascia, fat, and subcutaneous tissue before closure of the wound.. Duration Surgery. Concurrent medication/care: Intraoperatively, the patient was awake, sedated, or under light general anaesthetic depending on patient and anaesthetic factors. Indirectness: No indirectness (n=159) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthetic using bupivacaine.. Duration Surgery. Concurrent medication/care: Intraoperatively, the patient was awake, sedated, or under light general anaesthetic depending on patient and anaesthetic factors. Indirectness: No indirectness
Funding	Research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research programme (RP-PG-0407-10070)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER SURGERY) versus REGIONAL ANAESTHESIA

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: No pain on admission to recovery ward at .; Group 1: 115/163, Group 2: 111/159
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 ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Nausea at within 30 days - Actual outcome: Nausea and vomiting at During recovery from surgery; Group 1: 80/153, Group 2: 88/155 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 ; Group 1 Number missing: 10; Group 2 Number missing: 5	
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 days; Postoperative use of analgesia at as reported; Length of stay at .; Mobilisation within 24 hours after surgery at .

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Study	**Basques 2015[18]**
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=20936)
Countries and setting	Conducted in USA; Setting:
Line of therapy	Not applicable
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary elective total hip arthroplasty for osteoarthritis of the hip
Exclusion criteria	None detailed
Recruitment/selection of patients	American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database from 2010 to 2012.
Age, gender and ethnicity	Age - Other: 16% under 55, 30% 55-64, 31% 65-74, 24% 75 plus.. Gender (M:F): Define. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=12752) Intervention 1: General - General anaesthesia. General anaethesia. Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness (n=8184) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthesia. Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness
Funding	Funding not stated (Some conflicts of interest declared. One author in this study received a grant from the National Center for Advancing Translational Sciences of the National Institutes of Health (Award Number TL1TR000141). Funds were used to pay for salary and equipment.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA versus GENERAL ANAESTHESIA Protocol outcome 1: Mortality at within 90 days - Actual outcome: Death at Within 30 days of surgery; OR; 1.19 (95%CI 0.57 to 2.53, Comments: Propensity-adjusted multivariate logistic regression. Bivariate and propensity-adjusted multivariate regressions were used to compare the rates of adverse outcomes that occurred with general anesthesia and spinal anesthesia, using spinal anesthesia cases as the reference. Multivariate regression adjusted for baseline differences in patient demographic characteristics and comorbidities as well as the propensity score.); 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 ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at within 30 days; Postoperative pain at within 30 days; Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

ISBN 978-1-4731-3722-6

Study	**Chen 2010[40]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=92)
Countries and setting	Conducted in Taiwan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 12 weeks 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 osteonecrosis, aged 18 to 80 years old, undergoing unilateral THA
Exclusion criteria	Consent not given or unable to be given, neuropathic pain or sensory disorders in the leg, previous surgery of the hip, coagulation abnormalities, severe renal or hepatic impairment, chronic opioid users, known history of intolerance to study drugs.
Recruitment/selection of patients	August 2007 to March 2008
Age, gender and ethnicity	Age - Mean (SD): 52 (13) and 54 (14). Gender (M:F): 54/37. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Extra comments	. Administration of anti-inflammatory drugs suspended a week before.

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Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: General - General anaesthesia with local infiltration analgesia (during or after procedure). General anaesthesia with propofol and fentanyl. After closing of capsule people received subcutaneous injection of 12ml 0.5% bupivicaine. Then 2ml/h 0.5% bupivicaine for 48 hours. . Duration Surgery with 12 weeks follow up. Concurrent medication/care: Surgery was standardised technique through anterolateral approach. . Indirectness: No indirectness (n=46) Intervention 2: General - General anaesthesia. General anaesthesia with propofol and fentanyl. After closing of capsule people received subcutaneous injection of 12ml saline. Then 2ml/h saline for 48 hours. . Duration Surgery with 12 weeks follow up. Concurrent medication/care: Surgery was standardised technique through anterolateral approach. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER PROCEDURE) versus GENERAL ANAESTHESIA

Protocol outcome 1: Postoperative use of analgesia at as reported
- Actual outcome: Use of systemic meperidine at 3rd day after surgery; Group 1: mean 8 mg (SD 21); n=45, Group 2: mean 16 mg (SD 26); n=46
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: 1, Reason: Intraoperative fracture; Group 2 Number missing: 0

Protocol outcome 2: Length of stay at .
- Actual outcome: Length of hospital stay at .; Group 1: mean 4.6 days (SD 1.88); n=45, Group 2: mean 4.7 days (SD 1.88); n=46
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: 1, Reason: Intraoperative fracture; Group 2 Number missing: 0

Protocol outcome 3: Nausea at within 30 days days

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- Actual outcome: Nausea/vomiting at Within 3 days of surgery; Group 1: 12/45, Group 2: 16/46 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: 1, Reason: Intraoperative fracture; Group 2 Number missing: 0	
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	**Den hartog 2015[56]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Netherlands
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery and follow-up for 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis of the hip and ASA I-II for whom primary THA has been recommended.
Exclusion criteria	Mental illness, contraindication to spinal anaesthesia, neurological condition that might influence perception of pain, cardiovascular condition in the present or past, allergy to any study medications, alcohol or drug abuse, rheumatoid arthritis, high BMI.
Age, gender and ethnicity	Age - Mean (range): 64 (43-84) and 69 (49-85) and 68 (55-84). Gender (M:F): 36/38. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: ASA grade I or II
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after

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	surgery). Spinal anaesthesia using bupivacaine. Propofol used for sedation. LIA using ropivacaine and adrenaline in a periacetabular fashion after reaming the acetabulum, and then into the capsule and the gluteus minimus and medius muscles. The vastus lateralis muscle and tensor fascia lata were infiltrated after introducing the femoral component and the subcutaneous tissue just before would closure. . Duration Surgery and inpatient period. Concurrent medication/care: Postoperative oral medication consisted paracetamol, celecoxib, gabapentin, tramadol. Rescue medication through piritramide and extra celecoxib. . Indirectness: No indirectness (n=25) Intervention 2: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacaine. Propofol used for sedation. Reverse LIA using ropivacaine and adrenaline starting with subcutaneous tissue before incision, infiltration of the joint capsule, clockwise periarticular infiltration before reaming the acetabulum. . Duration Surgery and inpatient period. Concurrent medication/care: Postoperative oral medication consisted paracetamol, celecoxib, gabapentin, tramadol. Rescue medication through piritramide and extra celecoxib.. Indirectness: No indirectness (n=25) Intervention 3: Regional - Regional anaesthesia. Spinal anaesthesia using bupivacaine. Propofol used for sedation. Placebo LIA using saline in a periacetabular fashion after reaming the acetabulum, and then into the capsule and the gluteus minimus and medius muscles. The vastus lateralis muscle and tensor fascia lata were infiltrated after introducing the femoral component and the subcutaneous tissue just before would closure.. Duration Surgery and inpatient period. Concurrent medication/care: Postoperative oral medication consisted paracetamol, celecoxib, gabapentin, tramadol. Rescue medication through piritramide and extra celecoxib.. Indirectness: No indirectness
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER SURGERY) versus REGIONAL ANAESTHESIA Protocol outcome 1: Postoperative use of analgesia at as reported - Actual outcome: Rescue medication at 1 hour after surgery; Group 1: 6/25, Group 2: 2/16 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,	

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Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA differential; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Nausea at within 30 days days - Actual outcome: Nausea at Within 8 hours of surgery; Group 1: 2/25, Group 2: 2/25 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA differential; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA WITH REVERSE LOCAL INFILTRATION ANALGESIA (DURING OR AFTER SURGERY) versus REGIONAL ANAESTHESIA Protocol outcome 1: Postoperative use of analgesia at as reported - Actual outcome: Rescue medication at 1 hour after surgery; Group 1: 2/24, Group 2: 2/16 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA differential; Group 1 Number missing: 1, Reason: Converted to general; Group 2 Number missing: Protocol outcome 2: Nausea at within 30 days days - Actual outcome: Nausea at Within 8 hours of surgery; Group 1: 2/24, Group 2: 2/25 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA differential; Group 1 Number missing: 1, Reason: Converted to general; 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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Length of stay at .; Mobilisation within 24 hours after surgery at .

ISBN 978-1-4731-3722-6

Study	**Dobie 2012[61]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=96)
Countries and setting	Conducted in United Kingdom; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 2 days 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 degenerative or rheumatoid arthritis undergoing primary THA
Exclusion criteria	Treated by the study anesthetist, older than 85 years, cognitive impairment, history of allergy to the study medications, severe inflammatory polyarthritis, or American Society of Anesthesiologists (ASA) Class 4 or 5 physical status
Recruitment/selection of patients	Recruitment between October 2006 and February 2007.
Age, gender and ethnicity	Age - Mean (SD): 67 (10), 70 (8). Gender (M:F): Define. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness

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Interventions	(n=50) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia. Before wound closure, the group received local wound infiltration. 1mg levobupivacaine with adrenaline in 200 mL of saline, giving a final concentration of 0.125% levobupivacaine in 1:200000 adrenaline per milliliter. A total of 160 mL of this mixture was infiltrated into soft tissues as follows: 20 mL anteriorly to the lateral cutaneous nerve, 30 mL to the split fibers of the gluteus maximus, 20 mL to the capsule and piriformis, 30 mL inferiorly to the tensor fascia lata, 30 mL to the anterior subcutaneous border, and 30 mL to the posterior subcutaneous border.. Duration Unclear. Concurrent medication/care: Intrathecal isobaric bupivacaine, intravenous (IV) propofol, or midazolam to allow sedation to an appropriate depth. Morphine after surgery. . Indirectness: No indirectness (n=46) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthesia. Duration During surgery. Concurrent medication/care: Intrathecal isobaric bupivacaine, intravenous (IV) propofol, or midazolam to allow sedation to an appropriate depth. Morphine after surgery. . Indirectness: No indirectness
Funding	Funding not stated (Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER SURGERY) versus REGIONAL ANAESTHESIA

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Postoperative pain at 19-24 hours after surgery; Group 1: mean 0.68 (SD 0.89); n=46, Group 2: mean 0.98 (SD 0.89); n=46
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 ; Baseline details: No report of ASA; Group 1 Number missing: 4, Reason: Incorrect treatment given; Group 2 Number missing: 0

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: IV morphine use at 36 hours after surgery; Group 1: mean 13 mg (SD 12.7); n=46, Group 2: mean 15.1 mg (SD 12.7); n=46
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 ; Baseline details: No report of ASA; Group 1 Number missing: 4, Reason: Incorrect

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treatment given; Group 2 Number missing: 0 Protocol outcome 3: Length of stay at . - Actual outcome: Length of hospital stay at .; Group 1: mean 3.5 days (SD 2.22); n=46, Group 2: mean 3.9 days (SD 2.22); n=46 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 ; Baseline details: No report of ASA; Group 1 Number missing: 4, Reason: Incorrect treatment given; Group 2 Number missing: 0 Protocol outcome 4: Mobilisation within 24 hours after surgery at . - Actual outcome: Mobilisation on day 1 at .; Group 1: 41/46, Group 2: 40/46 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 ; Baseline details: No report of ASA; Group 1 Number missing: 4, Reason: Incorrect treatment given; Group 2 Number missing: 0	
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 days; Nausea at within 30 days days

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Study	**Donauer 2018[62]**
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=1713)
Countries and setting	Conducted in Multiple countries; Setting:
Line of therapy	Not applicable
Duration of study	Other:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who had hip replacement surgery under ICD 9 code: 81.54
Exclusion criteria	Missing information on anaesthesia or surgery
Recruitment/selection of patients	Analysis of people in the International PAIN OUT Registry. This takes data from institutions in Europe, Israel, and USA.
Age, gender and ethnicity	Age - Mean (SD): 63 (13) and 63 (11). Gender (M:F): Approximately 50% male. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Extra comments	Multivariate analysis included demographics, comorbidities, institution, year of surgery, type of regional anaesthesia, maximum/minimum pain, postoperative opioid consumption.

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Indirectness of population	No indirectness
Interventions	(n=574) Intervention 1: General - General anaesthesia. General anaesthesia. Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness (n=335) Intervention 2: Regional - Regional anaesthesia. Regional anaesthesia. Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness
Funding	Academic or government funding (Funded by the European Commission.)
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	**Duarte 2009[64]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in Brazil; Setting: Hospital Sarah in Brasília, Brazil.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 48 hours follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive people (ASA I to III) scheduled for THA
Exclusion criteria	Refused to participate in the study; had peripheral neuropathies, coagulopathies, or hypersensitivity to drugs used for analgesia; infection at the site of puncture; spinal deformities or history of spinal surgery; and those scheduled for review of the hip.
Recruitment/selection of patients	Recruited between March and September 2006
Age, gender and ethnicity	Age - Mean (SD): 61 (15) and 58 (16). Gender (M:F): 19/22. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=20) Intervention 1: General and regional - General and regional anaesthesia. General anaesthesia using alfentanil, propofol, and succinylcholine. Continuous epidural lumbar block using 0.5% ropivacaine. Duration Unclear. Concurrent medication/care: Premedicated with 5 mg of oral diazepam on the night before and the morning of the surgery. Indirectness: No indirectness (n=21) Intervention 2: General - General anaesthesia with nerve block. General anaesthesia using alfentanil, propofol, and succinylcholine. Posterior lumbar plexus block using 0.5% ropivacaine.. Duration Surgery. Concurrent medication/care: Premedicated with 5 mg of oral diazepam on the night before and the morning of the surgery. Indirectness: No indirectness
Funding	Funding not stated
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

ISBN 978-1-4731-3722-6

Study	**Eroglu 2005[66]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Turkey
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery and following 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People 50 - 80 years old and ASA I-III who were scheduled for primary unilateral total hip replacement.
Exclusion criteria	People with a bleeding disorder due to the use of aspirin or nonsteroidal anti-inflammatory drugs within 2 weeks of surgery, those with unstable angina, a hemodynamically significant aortic, valve or mitral valve stenosis (as documented by Doppler echocardiography or cardiac catheterization) and severe carotid artery stenosis (N70% occlusion), those with neurologic or cerebrovascular disease or psychiatric disease, those with unmedicated hypertension, and those in whom an epidural catheter had not been inserted
Age, gender and ethnicity	Age - Mean (SD): 64 (13) and 62 (10). Gender (M:F): 10/30. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=20) Intervention 1: Regional - Regional anaesthesia. Hypotensive epidural anesthesia (HEA). Combination of an extensive epidural block and an intravenous (IV) infusion of low-dose epinephrine.. Duration Surgery. Concurrent medication/care: Postoperative pain managed with PCA. . Indirectness: No indirectness (n=20) Intervention 2: General - General anaesthesia. Hypotensive total IV anaesthesia (HTIVA). Remifentanil infused for 2 minutes. Anaesthesia was induced with propofol. Vecuronium 0.1 mg d kg 1 was administered to achieve muscle relaxation before endotracheal intubation. Anesthesia was maintained with propofol infusion (125-250 lg d kg d min 1) and remifentanil infusion (0.5-3 lg d kg d min 1). Epinephrine 1 to 5 lg d min 1 IV was also infused.. Duration Surgery. Concurrent medication/care: Postoperative pain managed with PCA. . Indirectness: No indirectness
Funding	Funding not stated
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

ISBN 978-1-4731-3722-6

Study	**Fahs 2018[69]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in USA; Setting: One surgeon undertook all surgeries
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 weeks 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 primary osteoarthritis, undergoing unilateral primary THA via DAA by the senior surgeon.
Exclusion criteria	Children, prior ipsilateral hip surgery, lumbar instrumentation, acute trauma, rheumatoid arthritis, avascular necrosis, hip dysplasia, known sensitivity/allergy/contraindication to the anesthetic used, narcotic sensitivity, history of over 6 months of opioid dependency, peripheral neuropathy, and mental/cognitive impairment
Recruitment/selection of patients	May 2016 to May 2017.
Age, gender and ethnicity	Age - Mean (SD): 68 (8) and 65 (8). Gender (M:F): 51/48. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Not stated / Unclear

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Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: General - General anaesthesia with local infiltration analgesia (during or after procedure). General endotracheal anaesthesia (without neuraxial blockade) and periarticular anaesthetic soft-tissue infiltration. Periarticular anaesthetic soft-tissue infiltration was ropivacaine, epinephrine, morphine, and ketorolac diluted in saline injected after component implantation and before closure, into the tissues surrounding the hip joint. This included the joint capsule, rectus femoris direct and reflected heads, tensor fascia lata, and subcutaneous tissues circumferentially every 25mm.. Duration Surgery and postoperative time in hospital. Concurrent medication/care: Preoperatively, people received 2mg of intravenous midazolam, 50mcg of intravenous fentanyl, 400mg of oral celecoxib, and 1000mg of intravenous acetaminophen. Postoperative pain management was initiated in the PACU, consisting of IV hydromorphone and IV fentanyl in 0.25mg and 50mg increments, respectively, as needed.. Indirectness: No indirectness (n=50) Intervention 2: General - General anaesthesia with nerve block. General endotracheal anaesthesia (without neuraxial blockade) and psoas compartment block. 50mL of anaesthetic solution (ropivacaine in saline) was delivered into the psoas muscle compartment using an 18 gauge spinal needle, after the femoral neck osteotomy and head extraction.. Duration Surgery and postoperative time in hospital. Concurrent medication/care: Preoperatively, people received 2mg of intravenous midazolam, 50mcg of intravenous fentanyl, 400mg of oral celecoxib, and 1000mg of intravenous acetaminophen. Postoperative pain management was initiated in the PACU, consisting of IV hydromorphone and IV fentanyl in 0.25mg and 50mg increments, respectively, as needed.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER PROCEDURE) versus GENERAL ANAESTHESIA WITH NERVE BLOCK

Protocol outcome 1: Quality of life at within 30 days
- Actual outcome: Quality of recovery at Postoperative day 1; Group 1: mean 183.1 (SD 10.3); n=50, Group 2: mean 177.2 (SD 14); n=49; QoR-40 40-200 Top=High is good outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

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Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: 1, Reason: Unknown fracture Protocol outcome 2: Postoperative use of analgesia at as reported - Actual outcome: Narcotic consumption at By postoperative day 1; Group 1: mean 43 mg (SD 34); n=50, Group 2: mean 46.2 mg (SD 27.8); n=49 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 ; Group 1 Number missing: ; Group 2 Number missing: 1, Reason: Unknown fracture Protocol outcome 3: Length of stay at . - Actual outcome: Hospital length of stay at .; Group 1: mean 1.4 days (SD 0.6); n=50, Group 2: mean 1.4 days (SD 0.8); n=49 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 ; Group 1 Number missing: ; Group 2 Number missing: 1, Reason: Unknown fracture	
Protocol outcomes not reported by the study	Mortality at within 90 days; Postoperative pain at within 30 days; Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	**Gottschalk 2014-1[89]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in Germany; Setting:
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 aged 18-75 years old with ASA physical status I - III undergoing elective total hip replacement
Exclusion criteria	People undergoing revision hip replacement or bilateral surgery or with diabetes.
Recruitment/selection of patients	September 2008 to March 2011
Age, gender and ethnicity	Age - Mean (SD): 74 (6) and 71 (10). Gender (M:F): 17/23. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: General - General anaesthesia. Induced using sufentanil and propofol. Endo-tracheal

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	intubation used. Anaesthesia was maintained with sevoflurane. Inadequate anaesthesia (such as hypertension, tachycardia, patient movement) was treated with a sufentanil bolus. After anesthesia induction, people received an IV infusion of metamizole with saline.. Duration Surgery and postoperative hospital period. Concurrent medication/care: After surgery, people transferred to the PACU.. Indirectness: No indirectness (n=20) Intervention 2: Regional - Regional anaesthesia. The spinal block was performed with patients placed in the sitting position. After the lumbar spine region was disinfected, local anesthesia was performed using lidocaine.The spinal space was injected with bupivacaine. All people received an IV infusion of metamizole in saline.. Duration Surgery and hospital period. Concurrent medication/care: After surgery, people transferred to the PACU.. Indirectness: No indirectness
Funding	Academic or government funding (Supported by departmental funding only)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA versus GENERAL ANAESTHESIA Protocol outcome 1: Postoperative use of analgesia at as reported - Actual outcome: PACU analgesics: piritramide at Unclear; Group 1: mean 0.2 mg (SD 1); n=20, Group 2: mean 3.5 mg (SD 3.42); n=20 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 ; Baseline details: Specific ASA numbers not detailed; 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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	**Gottschalk 2014-2**[89]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Germany
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 with diabetes aged 18-75 years old with ASA physical status I - III undergoing elective total hip replacement
Exclusion criteria	People undergoing revision hip replacement or bilateral surgery
Recruitment/selection of patients	September 2008 to March 2011
Age, gender and ethnicity	Age - Mean (SD): 70 (8) and 73 (7). Gender (M:F): 14/14. Ethnicity: Not detailed
Further population details	1. Age: 2. ASA grade:
Indirectness of population	No indirectness

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Interventions	(n=15) Intervention 1: General - General anaesthesia. Induced using sufentanil and propofol. Endo-tracheal intubation used. Anaesthesia was maintained with sevoflurane. Inadequate anaesthesia (such as hypertension, tachycardia, patient movement) was treated with a sufentanil bolus. After anesthesia induction, people received an IV infusion of metamizole with saline.. Duration Surgery and postoperative hospital period. Concurrent medication/care: After surgery, people transferred to the PACU.. Indirectness: No indirectness (n=15) Intervention 2: Regional - Regional anaesthesia. The spinal block was performed with patients placed in the sitting position. After the lumbar spine region was disinfected, local anesthesia was performed using lidocaine.The spinal space was injected with bupivacaine. All people received an IV infusion of metamizole in saline.. Duration Surgery and hospital period. Concurrent medication/care: After surgery, people transferred to the PACU.. Indirectness: No indirectness
Funding	Academic or government funding (Supported by departmental funding only)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA versus GENERAL ANAESTHESIA Protocol outcome 1: Postoperative use of analgesia at as reported - Actual outcome: PACU analgesics: piritramide at Unclear; Group 1: mean 1.7 mg (SD 3.96); n=13, Group 2: mean 3.1 mg (SD 4.067); n=15 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Specific ASA numbers not detailed; Group 1 Number missing: 2, Reason: Change to general and massive haemorrhage; Group 2 Number missing: 0	
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	Goytizolo 2016[90]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=92)
Countries and setting	Conducted in USA
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 60 to 100 years old who could safely undergo neuraxial anaesthesia and ASA score I-III and scheduled for primary total hip arthroplasty
Exclusion criteria	Refusal to participate, surgery other than primary THR, chronic opioid use (defined as daily use of opioids for more than 3 months), allergy to study medications, and contraindication to CSE anesthesia or LPB (history of lumbar spinal fusion, bleeding disorder, use of clinically relevant anticoagulant or antiplatelet medications, anatomic abnormalities, infection at a potential injection site)
Age, gender and ethnicity	Age - Mean (SD): 70 (8) and 70 (11). Gender (M:F): 44/46. Ethnicity: Not detailed
Further population details	1. Age: 60 years or older 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=46) Intervention 1: Regional - Regional anaesthesia with nerve block. Combined spinal–epidural (CSE) anaesthesia with lumbar plexus block.. Duration Surgery and in hospital postoperative period. Concurrent medication/care: The patient-controlled epidural analgesia (PCEA) was started immediately upon arrival in the recovery room. Patients received a continuous infusion of 2 ml/h, with an additional bolus of 4 ml on demand and a lockout of 10 min with a 20 ml/h maximum.. Indirectness: No indirectness (n=46) Intervention 2: Regional - Regional anaesthesia. Combined spinal–epidural (CSE) anaesthesia . Duration Surgery and in hospital postoperative period . Concurrent medication/care: The patient-controlled epidural analgesia (PCEA) was started immediately upon arrival in the recovery room. Patients received a continuous infusion of 2 ml/h, with an additional bolus of 4 ml on demand and a lockout of 10 min with a 20 ml/h maximum.. Indirectness: No indirectness
Funding	Academic or government funding (This study was supported with funds from the Research and Education Fund of the Department of Anesthesiology at the Hospital for Special Surgery. Dr. Sandra Hurtado Rúa was partially supported by the following grant: Clinical Translational Science Center (CTSC) (UL1- RR024996).)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA WITH NERVE BLOCK versus REGIONAL ANAESTHESIA Protocol outcome 1: Postoperative use of analgesia at as reported - Actual outcome: PCA and oral opioid use at While in hospital; Group 1: mean 60 mg (SD 33); n=46, Group 2: mean 71 mg (SD 37); n=46 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 ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Nausea at within 30 days days - Actual outcome: People reporting nausea at Postoperative day 1; Group 1: 14/46, Group 2: 11/44 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 ; Group 1 Number missing: ; Group 2 Number missing: 2, Reason: Lost due to technical failure	
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; Thromboembolic complications at within 90 days;

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Hospital readmissions at within 30 days days; Length of stay at .; Mobilisation within 24 hours after surgery at .	

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Study	Green 2014[91]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=53)
Countries and setting	Conducted in Irish Republic; Setting: All procedures were performed by a single surgeon
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 scheduled for primary total hip replacement
Exclusion criteria	Allergy to local anaesthetics
Age, gender and ethnicity	Age - Mean (SD): Not detailed. Gender (M:F): Not detailed. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Not stated / Unclear
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia and psoas

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	compartment block was administered using an 18G spinal needle and 50 ml bupivacaine and saline.. Duration Surgery and in hospital period. Concurrent medication/care: Post-operatively, all people received regular paracetamol, Diclofenac and oxycontin. Oxynorm was prescribed for breakthrough pain as required on a four hourly basis.. Indirectness: No indirectness (n=27) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthesia.. Duration Surgery and in hospital period. Concurrent medication/care: Post-operatively, all people received regular paracetamol, Diclofenac and oxycontin. Oxynorm was prescribed for breakthrough pain as required on a four hourly basis.. Indirectness: No indirectness
Funding	Funding not stated

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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain at 2 hours after surgery; Group 1: mean 0.15 (SD 0.77); n=26, Group 2: mean 1.23 (SD 2.026); n=27; Numerical Rating Scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - 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: Time to request postoperative analgesia at .; Group 1: mean 324 minutes (SD 113.34); n=26, Group 2: mean 260.73 minutes (SD 202.98); n=27
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Mobilisation within 24 hours after surgery at .
- Actual outcome: Mobilisation at Postoperative day 1; Group 1: 22/26, Group 2: 24/27
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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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 days; Length of stay at .; Nausea at within 30 days days

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Study	**Harsten 2015[96]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Sweden; Setting: Hassleholm hospital in Sweden.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 2 days 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 scheduled for THA. ASA I-III, 45-85 years old.
Exclusion criteria	Previous surgery of same hip, obesity, rheumatoid arthritis, immunological depression, allergy to any study drugs, taking opioids or steroids, history of stroke or psychiatric disease.
Recruitment/selection of patients	January to May 2013
Age, gender and ethnicity	Age - Mean (SD): 68 (9), 66 (8). Gender (M:F): 60/58. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=60) Intervention 1: Regional - Regional anaesthesia. 3ml 0.5% bupivicaine utilised for spinal anaesthesia. . Duration Surgery and 3 days follow-up. Concurrent medication/care: Celecoxib and paracetamol given periodically. Propofol used for sedation. Patient controlled analgesia used post-operatively. . Indirectness: No indirectness (n=60) Intervention 2: General - General anaesthesia. General anaesthesia with remifentanil and propofol. . Duration Surgery and 3 days follow-up. Concurrent medication/care: Celecoxib and paracetamol given periodically. Propofol used for sedation. Patient controlled analgesia used post-operatively. . Indirectness: No indirectness
Funding	Academic or government funding (Institutional grants)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA versus GENERAL ANAESTHESIA Protocol outcome 1: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 30 hours (SD 7.4); n=58, Group 2: mean 26 hours (SD 7.4); n=60 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: 2, Reason: Converted to GA; Group 2 Number missing: 0 Protocol outcome 2: Mobilisation within 24 hours after surgery at . - Actual outcome: Able to walk 5 metres 12 hours after surgery at .; Group 1: 57/58, Group 2: 60/60 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: 2, Reason: Converted to GA; Group 2 Number missing: 0	
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Nausea at within 30 days days

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Study	**Haughom 2015[97]**
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=28857)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Other:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People having primary total hip arthroplasty.
Exclusion criteria	Primary diagnosis code of malignancy, mechanical complication, fracture, or infection. Wound classification other than 'clean'.
Recruitment/selection of patients	National Surgical Quality Improvement Database (NSQIP). It gathered data from 400 hospitals in 2012. This dataset was from 2005 to 2012.
Age, gender and ethnicity	Age - Mean (SD): 66 and 64. Gender (M:F): Approximately 45% male, 55% female. . Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=17540) Intervention 1: General - General anaesthesia. General anaesthesia. Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness (n=11317) Intervention 2: Regional - Regional anaesthesia. Spinal or epidural anaesthesia. Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness
Funding	Academic or government funding (Database funded by the American College of Surgeons)
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	**Hofstad 2015[101]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=116)
Countries and setting	Conducted in Norway; Setting: Orthopedic outpatient clinic of St. Olav's Hospital in Trondheim, Norway.
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery and inpatient period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People scheduled for elective primary THA regardless of age, ASA score, or type of prosthesis.
Exclusion criteria	Contraindications to spinal anesthesia, dexamethasone, or acetaminophen, people who were given general anaesthesia and who were operated with an approach different to standard direct lateral, people with osteosynthesis to be removed at the same operation.
Recruitment/selection of patients	March 2013 through March 2014
Age, gender and ethnicity	Age - Median (range): 65 (24-88) and 66 (49-85). Gender (M:F): 33/76. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=58) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia with bupivacaine. LIA consisted of 150mL ropivacaine and epinephrine (1 mg/mL). Local infiltration analgesia or placebo was injected in the periacetabular tissue after insertion of the acetabular component. After insertion of the femoral component, 50 mL was inserted in the gluteus muscles and the proximal part of the iliotibial tract. The last 50 mL was inserted in the subcutaneous layers.. Duration Surgery and inpatient period. Concurrent medication/care: Premedication cocktail consisting of dexamethasone, etoricoxib and acetaminophen. Propofol infusion was administered for sedation if required. Postoperative multimodal orally administered opioid-sparing analgesia was given: NSAIDS and acetaminophen were given at regular intervals and oxycodone was given if needed.. Indirectness: No indirectness (n=58) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthesia with bupivacaine. LIA placebo was 150mL saline. Local infiltration analgesia or placebo was injected in the periacetabular tissue after insertion of the acetabular component. After insertion of the femoral component, 50 mL was inserted in the gluteus muscles and the proximal part of the iliotibial tract. The last 50 mL was inserted in the subcutaneous layers.. Duration Surgery and inpatient period. Concurrent medication/care: Premedication cocktail consisting of dexamethasone, etoricoxib and acetaminophen. Propofol infusion was administered for sedation if required. Postoperative multimodal orally administered opioid-sparing analgesia was given: NSAIDS and acetaminophen were given at regular intervals and oxycodone was given if needed.. Indirectness: No indirectness
Funding	Funding not stated (Appears to be institutional funding.)
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	**Hogevold 2000[102]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=12)
Countries and setting	Conducted in Norway
Line of therapy	Not applicable
Duration of study	--: 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	People ASA I-II undergoing uncemented primary hip arthroplasty
Exclusion criteria	Not detailed
Age, gender and ethnicity	Age - Median (range): 53. Gender (M:F): Not detailed. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: ASA grade I or II
Indirectness of population	No indirectness
Interventions	(n=6) Intervention 1: Regional - Regional anaesthesia. Spinal/epidural anaesthesia using bipuvicaine. . Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness

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	(n=6) Intervention 2: General - General anaesthesia. Induced by IV thiopental, pancuronium, fentanyl. . Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness
Funding	Funding not stated
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	**Hunt 2013[105]**
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=409096)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Other:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary total hip replacement surgery
Exclusion criteria	Simultaneous bilateral operations, the person's NHS number was not traceable, consent had been withdrawn
Recruitment/selection of patients	Data taken from National Joint Registry from April 2003 to December 2011. The NHS Personal Demographics Service provided dates of death from the Office for National Statistics if the NHS number was traceable.
Age, gender and ethnicity	Age - Mean (SD): Most people were over 60 years old. Gender (M:F): Greater number of women than men represented. . Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed

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Indirectness of population	No indirectness
Interventions	(n=96433) Intervention 1: General - General anaesthesia. General anaesthesia. Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness (n=165807) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthesia. Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness
Funding	Academic or government funding (National Joint Registry for England and Wales.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA versus GENERAL ANAESTHESIA Protocol outcome 1: Mortality at within 90 days - Actual outcome: Mortality at Within 90 days of surgery; Group 1: n=165807 ; Group 2: n=96433; HR 0.85; Lower CI 0.74 to Upper CI 0.97; Test statistic: Cox proportional hazards model; Advantage to research or control? Advantage to research; Comments: Multivariate analysis including age and gender, mechanical and chemical thromboprophylaxis, and year of operation and approach, comorbidity, body-mass index, and comorbidity in conjunction with ethnic origin and social deprivation area. Multiple imputations for missing data, assuming that data were missing at random. 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 ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at within 30 days; Postoperative pain at within 30 days; Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	**Kratz 2015[132]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Germany; Setting: University of Marburg between May 2009 and May 2010
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 undergoing hip arthroplasty
Exclusion criteria	Surgery involving change of endoprotheses, under 40 years of age, ASA >2, expected intraoperative blood loss of more than 1000ml, clinically significant renal, cardiac or respiratory impairment.
Age, gender and ethnicity	Age - Mean (SD): 67 (12) and 66 (14). Gender (M:F): 24/28. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: ASA grade I or II
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: General - General anaesthesia with nerve block. General anaesthesia after supplemental femoral nerve block. Duration Surgery. Concurrent medication/care: .. Indirectness: No

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	indirectness (n=40) Intervention 2: General - General anaesthesia. General anaesthesia. Duration Surgery. Concurrent medication/care: .. Indirectness: No indirectness
Funding	No funding (No specific funding received)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL ANAESTHESIA WITH NERVE BLOCK versus GENERAL ANAESTHESIA Protocol outcome 1: Postoperative pain at within 30 days - Actual outcome: Postoperative pain at 24 hours after surgery; Group 1: mean 1.7 (SD 2.2); n=26, Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: Breach of study protocol; Group 2 Number missing: 14, Reason: Breach of study protocol Protocol outcome 2: Postoperative use of analgesia at as reported - Actual outcome: Cumulative dose of ibuprofen at .; Group 1: mean 69 mg (SD 200); n=26, Group 2: mean 292 mg (SD 490); n=26 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: Breach of study protocol; Group 2 Number missing: 14, Reason: Breach of study protocol	
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 days; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	**Kuchalik 2017[134]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in Sweden; Setting: Conducted at University Hospital, Orebro from September 2013 to December 2015.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and follow up after 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults 80 years old or younger and ASA I-III.
Exclusion criteria	Taking opiates preoperatively for pain relief, allergy to local anesthetic or contraindication to NSAIDs, re-operation THA, serious liver, kidney or heart diseases, known bleeding disorders, contraindications to spinal anaesthesia, participation in another clinical trial.
Age, gender and ethnicity	Age - Mean (SD): 64 (7) and 63 (8). Gender (M:F): 26/30. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=29) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacaine, LIA using ropivacaine, ketorloac and adrenaline. Injection around cup of acetabulum after it is in place. After fixing the femur component, injection into rotators. Final injection subcutaneously around the catheter. . Duration Surgery and in hospital period. . Concurrent medication/care: POstoperative care: paracetamol 4 times a day. PCA device using morphine. . Indirectness: No indirectness (n=27) Intervention 2: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia using bupivacaine, Femoral nerve block using ropivacaine. . Duration Surgery and in hospital period. . Concurrent medication/care: Postoperative care: paracetamol 4 times a day. PCA device using morphine. . Indirectness: No indirectness
Funding	Funding not stated (It was declared there were no conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER SURGERY) versus REGIONAL ANAESTHESIA WITH NERVE BLOCK

Protocol outcome 1: Postoperative use of analgesia at as reported
- Actual outcome: Postoperative morphine IV consumption at 0-24 hours after surgery; Group 1: mean 16.4 mg (SD 10.7); n=29, Group 2: mean 30 mg (SD 16.6); n=27
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 ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Nausea at within 30 days days
- Actual outcome: Nausea at 4-24 hours after surgery; Group 1: 12/29, Group 2: 15/27
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 ; 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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Length of stay at .; Mobilisation within 24 hours after surgery

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Study	**Liu 2011[140]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in China; Setting: Undertaken in the Orthopaedics Department of Changzheng Hospital (Shanghai, China) between October 2008 and March 2009.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 7 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 under 80 years of age with osteoarthritis, ASA I–III, normal or low body mass index, scheduled total primary unilateral hip arthroplasty under standard spinal anesthesia.
Exclusion criteria	Known allergy or intolerance to one of the study drugs; general anesthesia; regular opioid use; neuromuscular deficit; rheumatoid arthritis; and the inability to comprehend subjective pain scales such as the visual analog scale (VAS).
Age, gender and ethnicity	Age - Mean (SD): 74 (9). Gender (M:F): 19/61. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=40) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia. The LIA was composed of morphine, bupivacaine, betamethasone, and epinephrine, which were mixed with normal saline to make a combined amount of 60 mL. After implantation of the joint prosthesis, the joint capsule was injected (15 mL). After capsulorrhaphy, the gluteus maximus and medius, iliopsoas, and external rotators were infiltrated (20 mL) with care to protect the sciatic and femoral nerves and vessels. The synovium, fascia lata, and subcuticular tissues were injected with the remaining 25 mL, sparing the skin.. Duration Surgery and 7 days follow-up. Concurrent medication/care: To prevent insufficient analgesia, all people received patient-controlled analgesia (PCA) with morphine for the first 48 hours postoperatively. If pain still remained intolerable, an extra dose of 5–10 mg morphine was injected intramuscularly (and repeated if necessary) until a pain score of <30 mm was recorded. (n=40) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthesia. The LIA placebo was composed of 60ml of saline. After implantation of the joint prosthesis, the joint capsule was injected (15 mL). After capsulorrhaphy, the gluteus maximus and medius, iliopsoas, and external rotators were infiltrated (20 mL) with care to protect the sciatic and femoral nerves and vessels. The synovium, fascia lata, and subcuticular tissues were injected with the remaining 25 mL, sparing the skin.. Duration Surgery and 7 days follow-up. Concurrent medication/care: To prevent insufficient analgesia, all people received patient-controlled analgesia (PCA) with morphine for the first 48 hours postoperatively. If pain still remained intolerable, an extra dose of 5–10 mg morphine was injected intramuscularly (and repeated if necessary) until a pain score of <30 mm was recorded.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER SURGERY) versus REGIONAL ANAESTHESIA

Protocol outcome 1: Thromboembolic complications at within 90 days
- Actual outcome: DVT at 6-12 months; Group 1: 6/39, Group 2: 7/39
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA scales not detailed; Group 1 Number missing: 1, Reason: Cerebral infarction after 3 months; Group 2 Number missing: 1, Reason: Unable to contact

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Protocol outcome 2: Nausea at within 30 days days - Actual outcome: Nausea and vomiting at Unclear; Group 1: 8/40, Group 2: 18/40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA scales not detailed; Group 1 Number missing: 1, Reason: Cerebral infarction after 3 months; Group 2 Number missing: 1, Reason: Unable to contact	
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 days; Postoperative use of analgesia at as reported; Length of stay at .; Mobilisation within 24 hours after surgery at .

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Study	**Lunn 2011[143]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Denmark; Setting: Hvidovre hospital from September 2009 to March 2010.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Hospitalised period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults scheduled for elective unilateral primary total hip replacement. Performed by 1 of 3 orthopaedic surgeons.
Exclusion criteria	Alcohol and medical abuse, daily use of strong opioids or glucocorticoids, high BMI, allergies to local anaesthetics, pregnant or breastfeeding, diabetic neuropathy, rheumatoid arthritis, neurologic or psychiatric diseases that might influence pain perception.
Age, gender and ethnicity	Age - Mean (range): 67 (48-82) and 67 (35-87). Gender (M:F): 48/72. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=60) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Lumbar spinal anaesthesia with option of sedation with propofol. In addition there was intraoperative LIA using ropivacaine. . Duration Surgery. Concurrent medication/care: THA with posterior approach. Multimodal oral analgesic approach regimen utilised. . Indirectness: No indirectness (n=60) Intervention 2: Regional - Regional anaesthesia. Lumbar spinal anaesthesia with option of sedation with propofol.. Duration Surgery. Concurrent medication/care: THA with posterior approach. Multimodal oral analgesic approach regimen utilised. . Indirectness: No indirectness
Funding	Academic or government funding (Grant from the Lundbeck Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER SURGERY) versus REGIONAL ANAESTHESIA Protocol outcome 1: Postoperative use of analgesia at as reported - Actual outcome: Sufentanil in PACU at .; Group 1: 5/60, Group 2: 13/60 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 ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Mobilisation within 24 hours after surgery at . - Actual outcome: Walking at 8 hours after surgery; Group 1: 11/60, Group 2: 7/60 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 ; 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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Length of stay at .; Nausea at within 30 days days

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Study	**Maurer 2007[151]**
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=606)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Other:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary unilateral total hip replacement
Exclusion criteria	None detailed
Recruitment/selection of patients	January 1995 and January 1998 in the Hospital for Joint Diseases in New York, USA
Age, gender and ethnicity	Age - Mean (SD): 55 (16) and 63 (14). Gender (M:F): 276/330. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Indirectness of population	No indirectness
Interventions	(n=372) Intervention 1: Regional - Regional anaesthesia. Spinal anaesthesia normally using bupivavaine. .

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	Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness (n=234) Intervention 2: General - General anaesthesia. General anaesthesia with propofol used for induction. Duration Surgery. Concurrent medication/care: Not detailed. Indirectness: No indirectness
Funding	Funding not stated (Authors stated no conflicts of interest)
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	Modig 1987[162]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Sweden; Setting: Surgery by same othopaedic surgeon.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 24 hour 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 advanced osteoarthritis of the hip and ASA I or II who are scheduled to undergo total hip replacement.
Exclusion criteria	History of cardiac or pulmonary disease, rheumatoid arthritis, ankylosing spondylitis, Paget's disease, previous hip operations.
Age, gender and ethnicity	Age - Mean (SD): 67 (7), 68 (8), 65 (8). Gender (M:F): 18/20. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: ASA grade I or II
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Regional - Regional anaesthesia. Continuous lumbar epidural anaesthesia. Bupivicaine

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	and epinephrine used. . Duration Surgery. Concurrent medication/care: Oral diazepam 1 hour prior to surgery. Postoperative pain relief through bupivicaine and epinephrine on a 3-4 hourly basis. . Indirectness: No indirectness (n=10) Intervention 2: General - General anaesthesia. Inhalational general anaesthesia induced by IV thiopentone after IV atropine. . Duration Surgery and 24 hours follow-up. Concurrent medication/care: Oral diazepam 1 hour prior to surgery. Postoperative pain treatment consisted of ketobemidone on demand in 24 hours after surgery. . Indirectness: No indirectness (n=14) Intervention 3: General - General anaesthesia. Intermittent positive pressure ventilation (IPPV) general aneasthesia. Induced by IV thiopentone after IV atropine. . Duration Surgery and 24 hours follow-up. Concurrent medication/care: Oral diazepam 1 hour prior to surgery. Postoperative pain treatment consisted of ketobemidone on demand in 24 hours after surgery. . Indirectness: No indirectness
Funding	Academic or government funding (Grants from Swedish National Association Against Heart and Chest Diseases)
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	Murphy 2012[165]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=91)
Countries and setting	Conducted in Irish Republic; Setting: Conducted between February 2009 and February 2010.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 72 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 undergoing primary hip arthroplasty for osteoarthritis
Exclusion criteria	People with cognitive impairment, neurologic disorders, advanced liver or renal impairment, known ischemic heart disease, previous diagnosis of a chronic pain syndrome, opiate dependence, or any postoperative surgical or medical complications.
Age, gender and ethnicity	Age - Mean (SD): 54 (15) and 57 (11). Gender (M:F): 51/39. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after

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	surgery). Spinal anaesthetic using bupivacaine. One hundred fifty milligrams of levobupivacaine in 60mL saline was injected intraoperatively through the medial and anterior capsular spaces in the region of the obturator and femoral nerves and also around the short external rotators and gluteus maximus in the region of the inferior and superior gluteal nerves. This was infiltrated after insertion of the acetabular component and before insertion of the femoral stem. Ten milliliters then was infiltrated around the tensor fascia lata and subcutaneously before closing the wound.. Duration Surgery and in hospital postoperative period. Concurrent medication/care: Preoperative analgesia consisted of intravenous paracetamol and per rectum diclofenac at induction. Opioid analgesia via a PCA device for the initial 48 hours after surgery before conversion to a standard postoperative regime of paracetamol, diclofenac, and regular oral opioids.. Indirectness: No indirectness (n=46) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthetic using bupivacaine. Placebo: 60mL saline was injected intraoperatively through the medial and anterior capsular spaces in the region of the obturator and femoral nerves and also around the short external rotators and gluteus maximus in the region of the inferior and superior gluteal nerves. This was infiltrated after insertion of the acetabular component and before insertion of the femoral stem. Ten milliliters then was infiltrated around the tensor fascia lata and subcutaneously before closing the wound.. Duration Surgery and in hospital postoperative period. Concurrent medication/care: Preoperative analgesia consisted of intravenous paracetamol and per rectum diclofenac at induction. Opioid analgesia via a PCA device for the initial 48 hours after surgery before conversion to a standard postoperative regime of paracetamol, diclofenac, and regular oral opioids.. Indirectness: No indirectness
Funding	Funding not stated (Each author certified that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER SURGERY) versus REGIONAL ANAESTHESIA Protocol outcome 1: Postoperative use of analgesia at as reported - Actual outcome: PCA delivered morphine consumption at 48 hours after surgery; Group 1: mean 11.46 mg (SD 8.03); n=45, Group 2: mean 21.23 mg (SD	

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12.12); n=46 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 pain at within 30 days; Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

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Study	**Nicholson 2002[171]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=36)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery and inpatient period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Women aged over 55 years who had been amenorrhoeic for at least 2 years (including those on hormone replacement therapy) undergoing primary total hip replacement.
Exclusion criteria	Suffering from diseases or metabolic disorders known to alter bone metabolism, or were taking drugs known to affect bone metabolism: malignancies with bony metastases; renal failure; chronic liver disease; diabetes mellitus; rheumatoid arthritis; corticosteroids; anticonvulsants.
Age, gender and ethnicity	Age - Mean (SD): 76 (8) and 75 (8) and 78 (8). Gender (M:F): All female. Ethnicity: Not detailed
Further population details	1. Age: 60 years or older 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness

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Interventions	(n=12) Intervention 1: General - General anaesthesia. After a baseline blood sample was obtained, anaesthesia was induced with fentanyl and propofol, and the lungs were ventilated with iso¯urane and nitrous oxide in oxygen. Tracheal intubation was undertaken after administration of vecuronium.. Duration Surgery and inpatient period. Concurrent medication/care: People received intravenous morphine in doses up to 3 mg during surgery at the discretion of the anaesthetist. Postoperative analgesia was provided by intramuscular morphine and oral non-steroidal analgesics. All people were routinely given paracetamol for the duration of their hospital stay; some received additional analgesia with diclofenac after surgery.. Indirectness: No indirectness (n=12) Intervention 2: General - General anaesthesia. After a baseline blood sample was obtained, anaesthesia was induced with fentanyl and etomidate. and the lungs were ventilated with iso¯urane and nitrous oxide in oxygen. Tracheal intubation was undertaken after administration of vecuronium.. Duration Surgery and inpatient period. Concurrent medication/care: People received intravenous morphine in doses up to 3 mg during surgery at the discretion of the anaesthetist. Postoperative analgesia was provided by intramuscular morphine and oral non-steroidal analgesics. All people were routinely given paracetamol for the duration of their hospital stay; some received additional analgesia with diclofenac after surgery.. Indirectness: No indirectness (n=12) Intervention 3: General - General anaesthesia with nerve block. In the propofol/regional analgesia group, a three-in-one nerve block (femoral nerve, lateral cutaneous nerve of thigh and obturator nerve) was performed. A total of up to 30 ml of lidocaine and bupivacaine was administered. Tracheal intubation was then undertaken after the administration of vecuronium. . Duration Sugrery and inpatient period. Concurrent medication/care: People received intravenous morphine in doses up to 3 mg during surgery at the discretion of the anaesthetist. Postoperative analgesia was provided by intramuscular morphine and oral non-steroidal analgesics. All people were routinely given paracetamol for the duration of their hospital stay; some received additional analgesia with diclofenac after surgery.. Indirectness: No indirectness
Funding	Funding not stated
Protocol outcomes not reported by the	Mortality at within 90 days; Quality of life at within 30 days; Postoperative pain at within 30 days;

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study	Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

ISBN 978-1-4731-3722-6

Study	**Titman 2018[222]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Sweden; Setting: Undertaken in a hospital in southern Sweden during the period of February 1st to October 31st 2016.
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 ASA I-III scheduled for elective cemented THA.
Exclusion criteria	People with a lengthy increased opioid intake prior to surgery, known allergy to the medications used, <65 kg bodyweight, obesity with body mass index> 35 and inability to follow verbal or written instructions.
Age, gender and ethnicity	Age - Mean (SD): 76 (7) and 77 (6). Gender (M:F): 16/19. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Mixed
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: General - General anaesthesia with local infiltration analgesia (during or after

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	procedure). General anaesthesia via target controlled infusion (TCI) with Propofol and Remifentanil. 150ml mixture with ropivacaine and saline injected into the periarticular tissues in the following way: the first injection around the cup of the acetabulum when it was in place. When the femur component was fixed, the analgesic mixture was injected into the surrounding tissue focusing on the joint capsule, the gluteal and the adductor muscles. The last injection was made subcutaneously.. Duration Surgery and in hospital period. Concurrent medication/care: Pain relief: 1330mg Paracetamol-modified release orally three times a day, starting on the morning of surgery and continuing until discharge from the hospital. 200mg of Celecoxib was given orally prior to surgery and repeated in 12 hourly intervals.Oxycodone 10 mg was given i.v. 30 min prior to extubating. If the patient in the PACU had an NRS score at rest >4, morphine was repeatedly administered intravenously as often as needed until the NRS score was <3 prior to connecting the PCA device. All patients were provided with a PCA device programmed to deliver a morphine bolus of 2 mg, a lock-out of 10 min, and a maximum of 10 mg/h as a rescue medication for 24 h after the surgery.. Indirectness: No indirectness (n=20) Intervention 2: General - General anaesthesia. General anaesthesia via target controlled infusion (TCI) with Propofol and Remifentanil.. Duration Surgery and in hospital period. Concurrent medication/care: Pain relief: 1330mg Paracetamol-modified release orally three times a day, starting on the morning of surgery and continuing until discharge from the hospital. 200mg of Celecoxib was given orally prior to surgery and repeated in 12 hourly intervals.Oxycodone 10 mg was given i.v. 30 min prior to extubating. If the patient in the PACU had an NRS score at rest >4, morphine was repeatedly administered intravenously as often as needed until the NRS score was <3 prior to connecting the PCA device. All patients were provided with a PCA device programmed to deliver a morphine bolus of 2 mg, a lock-out of 10 min, and a maximum of 10 mg/h as a rescue medication for 24 h after the surgery. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER PROCEDURE) versus GENERAL ANAESTHESIA	

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Protocol outcome 1: Postoperative neurocognitive decline at within 30 days - Actual outcome: Neurological complications at 10 days after surgery; Group 1: 0/19, Group 2: 0/16 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 4 Protocol outcome 2: Postoperative use of analgesia at as reported - Actual outcome: Mophine consumption at 24 hours after arrival at PACU; Group 1: mean 16 ml (SD 12); n=19, Group 2: mean 13 ml (SD 9); n=16 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 4	
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

ISBN 978-1-4731-3722-6

Study	**Twyman 1990[224]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Women with osteoarthritis undergoing cemented primary total hip replacement
Exclusion criteria	Not detailed
Age, gender and ethnicity	Age - Mean (SD): Not detailed. Gender (M:F): All women. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: General - General anaesthesia with nerve block. Normotensive general anaesthesia. Lumbar plexus block. . Duration Surgery and inpatient period. Concurrent medication/care: Not detailed. Indirectness: No indirectness

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	(n=10) Intervention 2: General - General anaesthesia. Normotensive general anaesthesia.. Duration Surgery and inpatient period. Concurrent medication/care: Not detailed. Indirectness: No indirectness
Funding	No funding
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days days; Mobilisation within 24 hours after surgery at .

ISBN 978-1-4731-3722-6

Study	Villatte 2016[230]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in France; Setting: Single university city hospital over 18 months
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 2 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People 50 to 85 years old with degenerative hip disease or rheumatoid arthritis
Exclusion criteria	Refusal to participate, or lack of ability to provide informed consent, previous surgery of the hip joint or femoral neck fracture, known history of intolerance to study medication, general contraindication to surgery.
Age, gender and ethnicity	Age - Mean (SD): 67. Gender (M:F): 82/68. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: General - General anaesthesia with local infiltration analgesia (during or after

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	procedure). General anaesthesia with standardised protocol: a combination of hypnotic, opioid and curare. Local infiltration analgesia with ropivicaine and epinephrine administered twice: in the periarticular muscle and joint capsule just after opening the fascia and in the wound and subcutaneous tissue at the end of the procedure. . Duration Surgery with 48 hours follow-up. Concurrent medication/care: 3 surgeons performed all procedures with an anterolateral approach. Postoperative pain relief with paracetamol, ketoprofen, and patient controlled analgesia with morphine. . Indirectness: No indirectness (n=75) Intervention 2: General - General anaesthesia. General anaesthesia with standardised protocol: a combination of hypnotic, opioid and curare.. Duration Surgery with 48 hours follow-up. Concurrent medication/care: 3 surgeons performed all procedures with an anterolateral approach. Postoperative pain relief with paracetamol, ketoprofen, and patient controlled analgesia with morphine. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER PROCEDURE) versus GENERAL ANAESTHESIA

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain at 4 hours after surgery; Group 1: mean 2.39 (SD 1.51); n=75, Group 2: mean 2.87 (SD 1.55); n=75; Visual Analogue Scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA score not stated; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Analgesic consumption at 48 hours after surgery; Group 1: mean 20.9 mg (SD 20.8); n=75, Group 2: mean 24.4 mg (SD 19.7); n=75
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 ; Baseline details: ASA score not stated; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Length of stay at . - Actual outcome: Length of hospital stay at .; Group 1: mean 7.5 days (SD 0.93); n=75, Group 2: mean 7.6 days (SD 0.93); n=75 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 ; Baseline details: ASA score not stated; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Mobilisation within 24 hours after surgery at . - Actual outcome: Time to mobilisation at .; Group 1: mean 1.8 days (SD 0.93); n=75, Group 2: mean 1.9 days (SD 0.93); n=75 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 ; Baseline details: ASA score not stated; 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 days; Nausea at within 30 days days

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Study	**Zoric 2014[238]**
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in France; Setting: Orthopaedics ward at university hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and follow-up for 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged from 18 to 80 years old undergoing primary homolateral THA by postero-lateral incision under general anaesthesia, with a general health state permitting independent ambulation after surgery, capable of understanding the usage of patient controlled analgesia (PCA).
Exclusion criteria	Chronic renal disease, severe liver dysfunction, known allergy, intolerance to or counter-indication for drugs used in the study, long-term morphine treatment, pregnancy or breastfeeding, and reoperation
Age, gender and ethnicity	Age - Range: 38-70 and 42-80. Gender (M:F): 24/34. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed
Indirectness of population	No indirectness

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Interventions	(n=30) Intervention 1: General - General anaesthesia with local infiltration analgesia (during or after procedure). Standardised general anaesthesia. Administration of anaesthetic drugs was left to the discretion of the attending physician and based on usual monitoring. LIA using ropivacaine after putting in the implants. 40ml in the deep tissues: capsula, gluteus maximus and medius muscles, and rotating muscles. 40ml in the superficial tissues: fascia, subcutaneous tissues, and skin.. Duration Surgery. Concurrent medication/care: Postoperative period: on the day of surgery and the first postoperative day, IV analgesia consisted of paracetamol, nefopam, morphine titration depending on pain score, in the case of persistence of a high VAS evaluation NSAIDs can be used, a PCA device initiated.. Indirectness: No indirectness (n=31) Intervention 2: General - General anaesthesia. Standardised general anaesthesia. Administration of anaesthetic drugs was left to the discretion of the attending physician and based on usual monitoring. LIA placebo using saline after putting in the implants. 40ml in the deep tissues: capsula, gluteus maximus and medius muscles, and rotating muscles. 40ml in the superficial tissues: fascia, subcutaneous tissues, and skin.. Duration Surgery and inpatient period. Concurrent medication/care: Postoperative period: on the day of surgery and the first postoperative day, IV analgesia consisted of paracetamol, nefopam, morphine titration depending on pain score, in the case of persistence of a high VAS evaluation NSAIDs can be used, a PCA device initiated.. Indirectness: No indirectness
Funding	Academic or government funding (Institutional funding)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER PROCEDURE) versus GENERAL ANAESTHESIA

Protocol outcome 1: Postoperative use of analgesia at as reported
- Actual outcome: Postanaesthesia care unit (PACU) NSAID use at Inpatient period; Group 1: 4/29, Group 2: 4/29
Risk of bias: All domain - Very high, Selection - Very 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: 1; Group 2 Number missing: 2

Protocol outcome 2: Nausea at within 30 days days
- Actual outcome: Nausea at During 0-5 postoperative days; Group 1: 9/29, Group 2: 10/29
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

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Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 Protocol outcome 3: Mobilisation within 24 hours after surgery at . - Actual outcome: Walk in the corridor at Postoperative day 2; Group 1: 3/29, Group 2: 3/29 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Walking 24 hours after surgery not reported; Group 1 Number missing: 1; Group 2 Number missing: 2	
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; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days days; Length of stay at .

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Appendix E: Forest plots

E.1 Regional anaesthesia with nerve block versus regional anaesthesia

Figure 2: Postoperative pain within 30 days

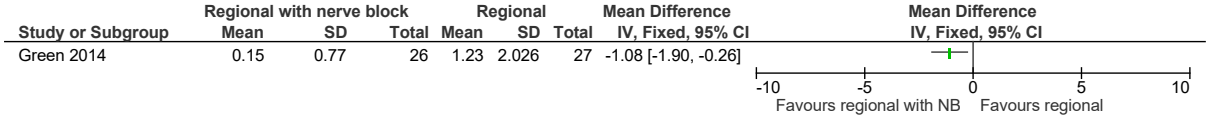


Figure 3: Postoperative use of analgesia

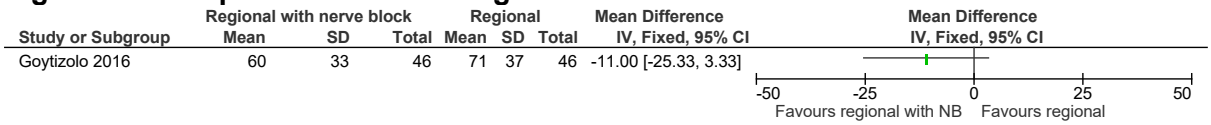


Figure 4: Time to postoperative use of analgesia

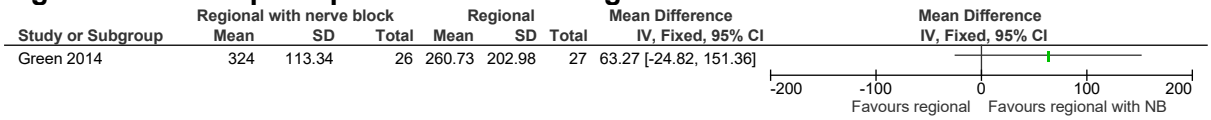


Figure 5: Nausea within 30 days

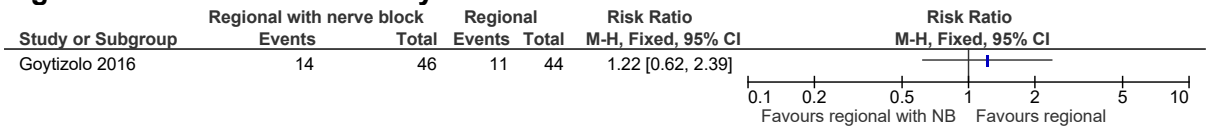
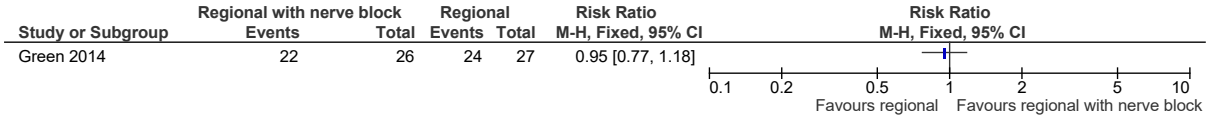


Figure 6: Mobilisation within 24 hours after surgery



E.2 Regional anaesthesia with LIA versus regional anaesthesia with nerve block

Figure 7: Postoperative use of analgesia

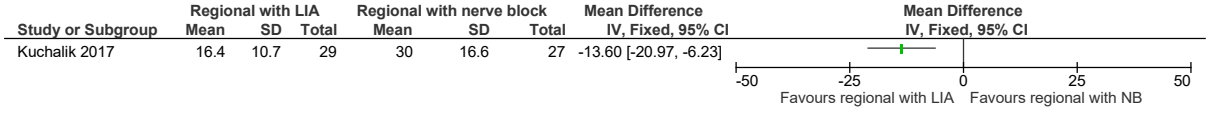
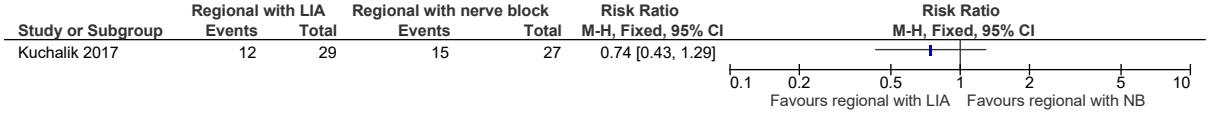


Figure 8: Nausea within 30 days



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E.3 Regional anaesthesia with LIA versus regional anaesthesia

Figure 9: Postoperative pain within 30 days

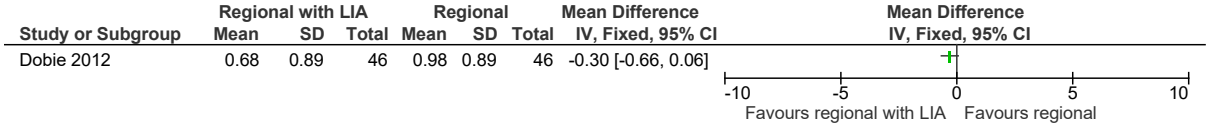

Figure 10: Postoperative pain: no pain on admission to recovery ward

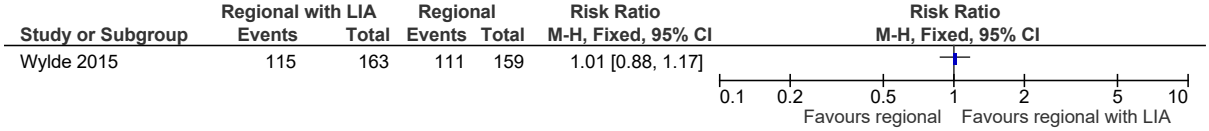

Figure 11: Thromboembolic complications within 90 days

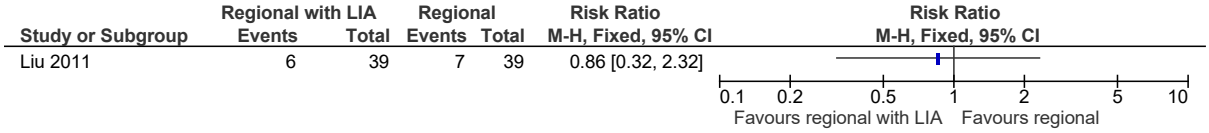

Figure 12: Postoperative use of analgesia

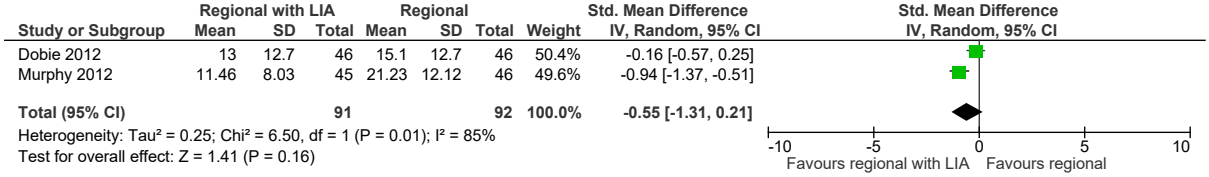

Figure 13: Number of people with postoperative use of analgesia

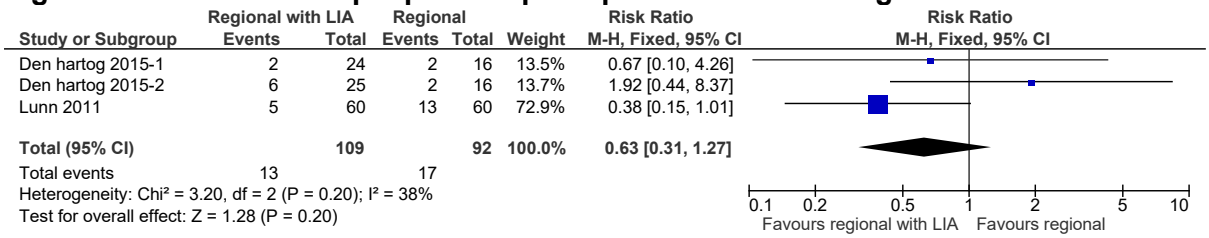

Figure 14: Length of stay

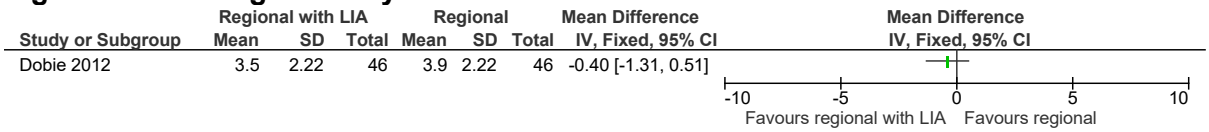

Figure 15: Nausea within 30 days

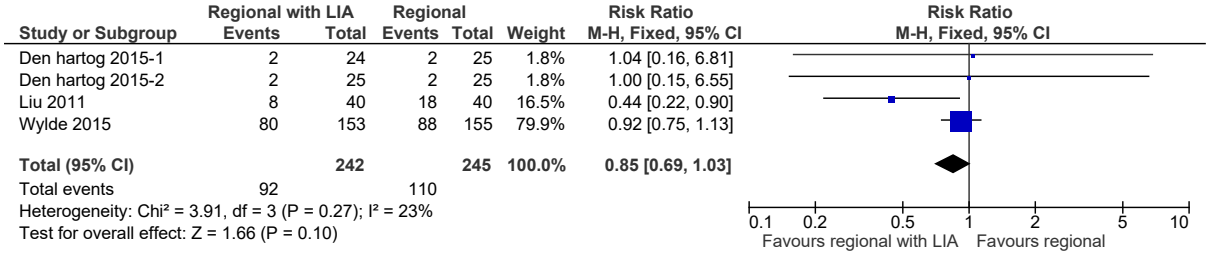

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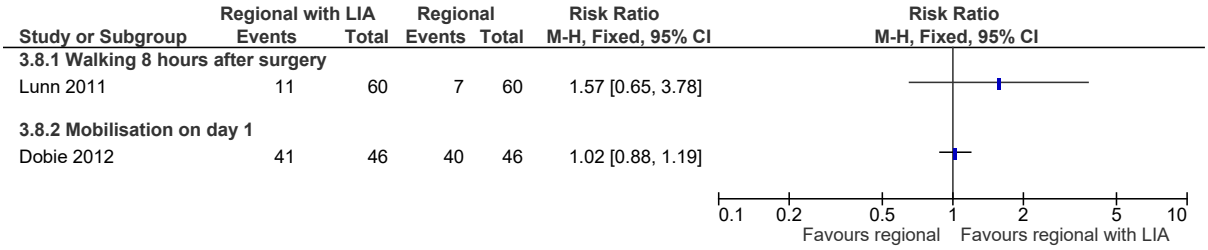
Figure 16: Mobilisation within 24 hours after surgery



E.4 Regional anaesthesia versus general anaesthesia

Figure 17: Mortality within 90 days of surgery

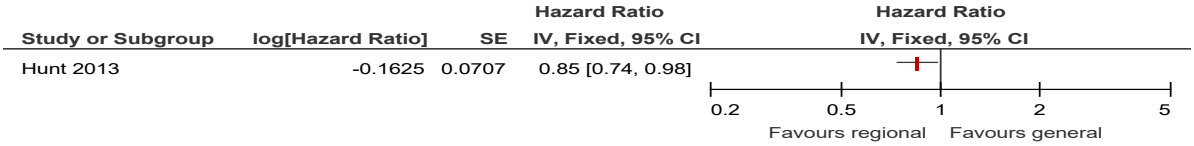


Figure 18: Mortality within 30 days of surgery

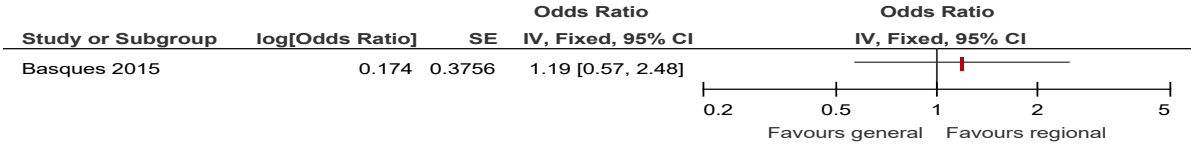


Figure 19: Postoperative use of analgesia

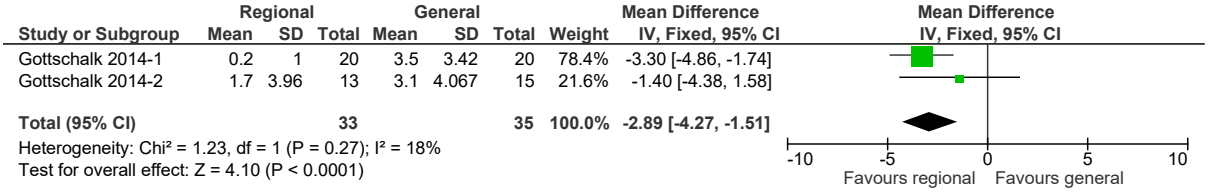


Figure 20: Length of stay

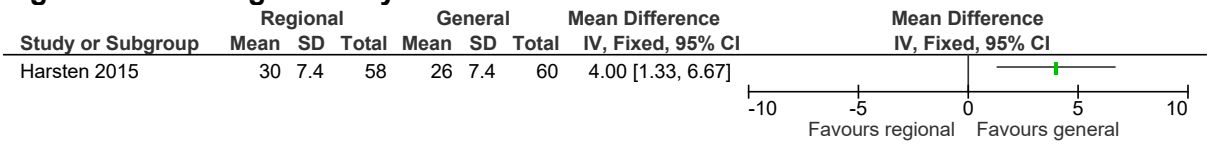
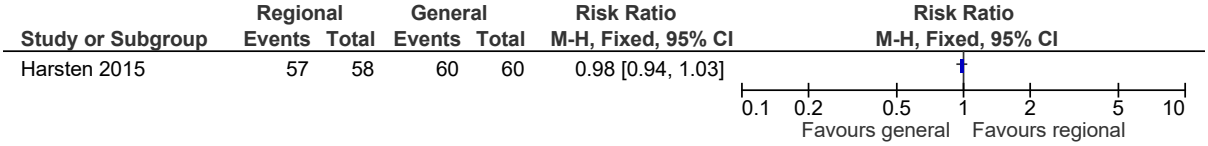


Figure 21: Mobilisation within 24 hours after surgery



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E.5 General anaesthesia with LIA versus general anaesthesia with nerve block

Figure 22: Quality of life within 30 days

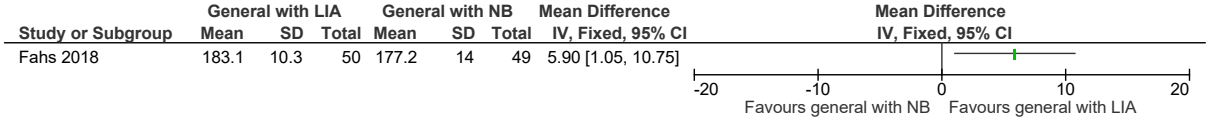


Figure 23: Postoperative use of analgesia

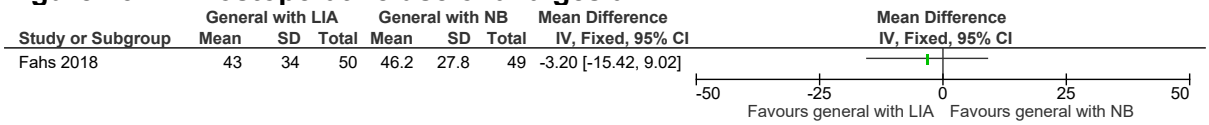
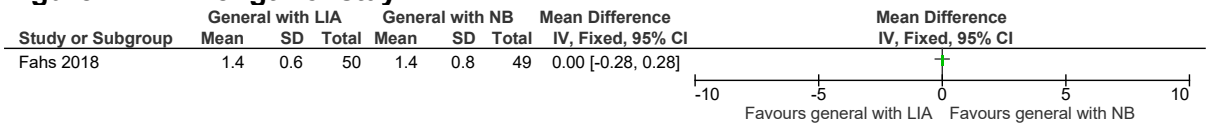


Figure 24: Length of stay



E.6 General anaesthesia with LIA versus general anaesthesia

Figure 25: Postoperative pain within 30 days

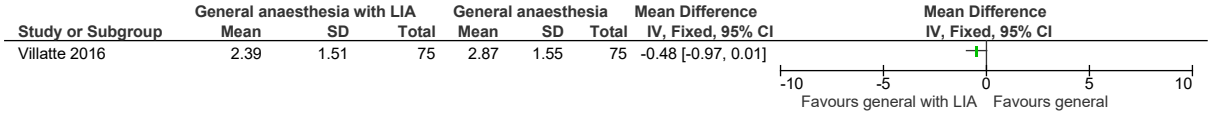


Figure 26: Postoperative neurocognitive decline within 30 days

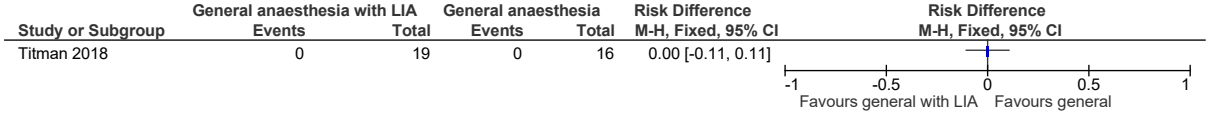


Figure 27: Postoperative use of analgesia

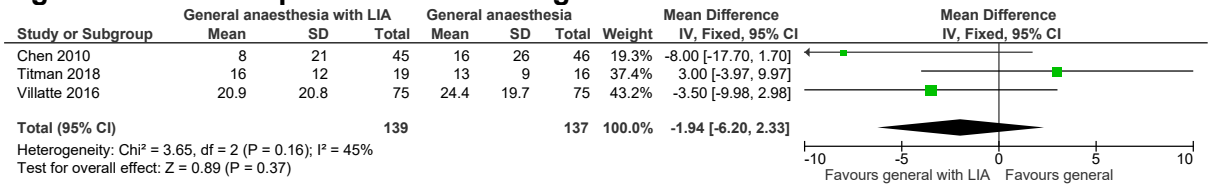


Figure 28: Number of people using postoperative NSAIDs

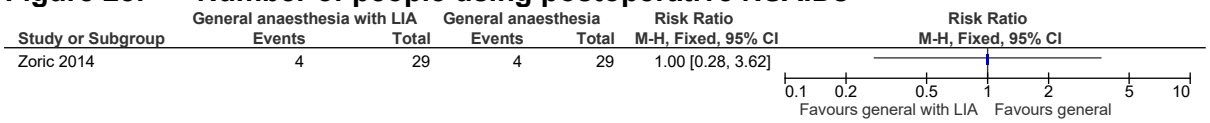


Figure 29: Length of stay

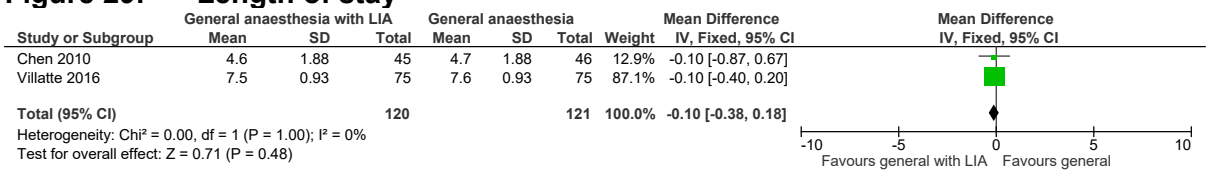


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Figure 30: Nausea within 30 days

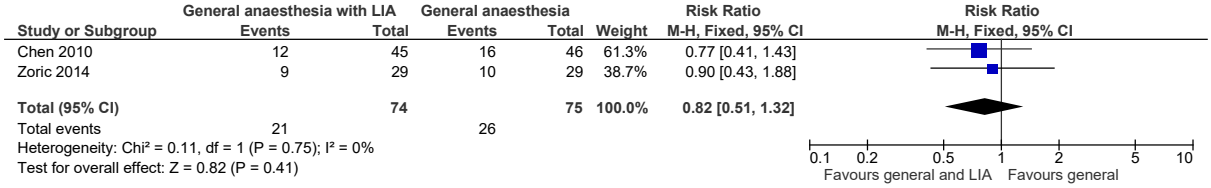


Figure 31: Mobilisation within 24 hours after surgery

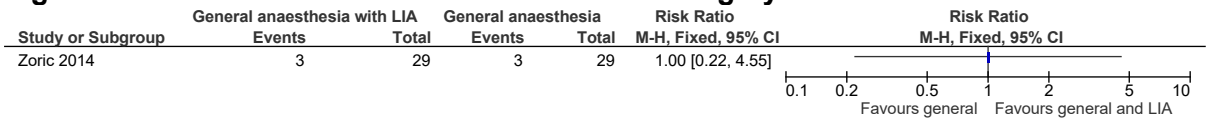
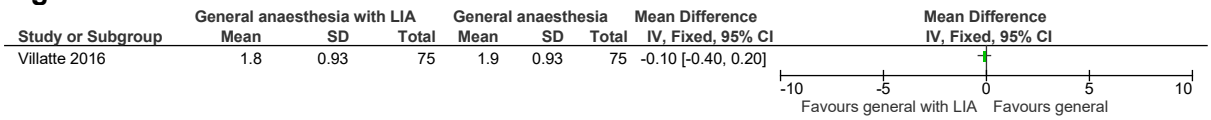


Figure 32: Time to mobilisation



E.7 General anaesthesia with nerve block versus general anaesthesia

Figure 33: Postoperative pain within 30 days

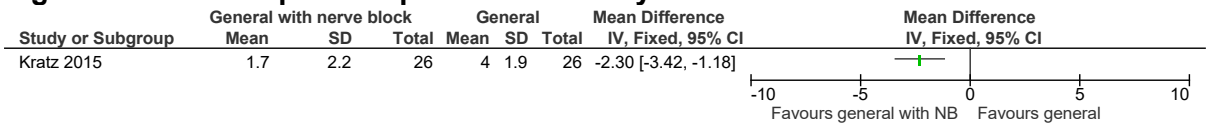
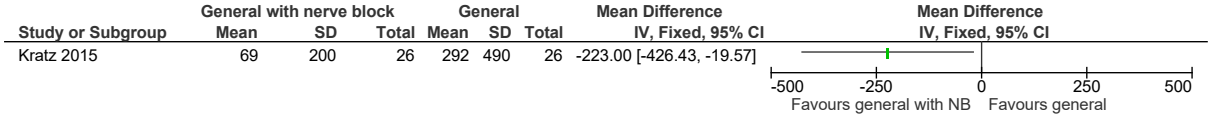


Figure 34: Postoperative use of analgesia



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Appendix F: GRADE tables

Table 19: Clinical evidence profile: regional anaesthesia with nerve block versus regional anaesthesia

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regional anaesthesia with nerve block versus regional anaesthesia	Control	Relative (95% CI)	Absolute		
Postoperative pain within 30 days (follow-up mean 2 hours after surgery; measured with: numerical rating scale; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	27	-	MD 1.08 lower (1.9 to 0.26 lower)	⊕OOO VERY LOW	CRITICAL
Postoperative use of analgesia (follow-up during hospital stay; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	46	46	-	MD 11 lower (25.33 lower to 3.33 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Time to postoperative use of analgesia (Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	27	-	MD 63.27 higher (24.82 lower to 151.36 higher)	⊕OOO VERY LOW	IMPORTANT
Nausea within 30 days (follow-up mean 1 days)												

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1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	14/46 (30.4%)	11/44 (25%)	RR 1.22 (0.62 to 2.39)	55 more per 1000 (from 95 fewer to 348 more)	⊕⊕OO LOW	IMPORTANT
Mobilisation within 24 hours after surgery												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/26 (84.6%)	24/27 (88.9%)	RR 0.95 (0.77 to 1.18)	44 fewer per 1000 (from 204 fewer to 160 more)	⊕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.

Table 20: Clinical evidence profile: regional anaesthesia with LIA versus regional anaesthesia with nerve block

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Regional anaesthesia with LIA versus regional anaesthesia with nerve block**	**Control**	**Relative (95% CI)**	**Absolute**		
Postoperative use of analgesia (follow-up 0-24 hours after surgery; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	29	27	-	MD 13.6 lower (20.97 to 6.23 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Nausea within 30 days days (follow-up 4-24 hours after surgery)												

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1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12/29 (41.4%)	15/27 (55.6%)	RR 0.74 (0.43 to 1.29)	144 fewer per 1000 (from 317 fewer to 161 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 21: Clinical evidence profile: regional anaesthesia with LIA versus regional anaesthesia

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Regional anaesthesia with LIA versus regional anaesthesia**	**Control**	**Relative (95% CI)**	**Absolute**		
Postoperative pain within 30 days (follow-up 19-24 hours after surgery; measured with: Visual Analogue Scale; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	46	-	MD 0.3 lower (0.66 lower to 0.06 higher)	⊕⊕OO LOW	CRITICAL
Postoperative pain (assessed with: no pain on admission to recovery ward)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	115/163 (70.6%)	111/159 (69.8%)	RR 1.01 (0.88 to 1.17)	7 more per 1000 (from 84 fewer to 119 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Thromboembolic complications within 90 days (follow-up mean 6-12 months)												
1	randomised	no serious	no serious	no serious	very serious[2]	none	6/39	7/39	RR 0.86 (0.32 to	25 fewer per 1000 (from 122 fewer to	⊕⊕OO	CRITICAL

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	trials	risk of bias	inconsistency	indirectness			(15.4%)	(17.9%)	2.32)	237 more)	LOW	
Postoperative use of analgesia (follow-up mean 3.5 days; measured with: mg; range of scores: 0-1; Better indicated by lower values)												
2	randomised trials	serious[1]	very serious[3]	no serious indirectness	serious[2]	none	91	92	-	SMD 0.55 lower (1.31 lower to 0.21 higher)	⊕OOO VERY LOW	IMPORTANT
Number of people with postoperative use of analgesia (follow-up at varying in-hospital time points)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	13/109 (11.9%)	17/92 (18.5%)	RR 0.63 (0.31 to 1.27)	68 fewer per 1000 (from 127 fewer to 50 more)	⊕⊕OO LOW	IMPORTANT
Length of stay (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	46	-	MD 0.4 lower (1.31 lower to 0.51 higher)	⊕OOO VERY LOW	IMPORTANT
Nausea within 30 days (follow-up unclear)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	92/242 (38%)	110/245 (44.9%)	RR 0.85 (0.69 to 1.03)	67 fewer per 1000 (from 139 fewer to 13 more)	⊕⊕⊕O MODERATE	IMPORTANT
Mobilisation on day 1 after surgery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/46 (89.1%)	40/46 (87%)	RR 1.02 (0.88 to 1.19)	17 more per 1000 (from 104 fewer to 165 more)	⊕⊕⊕O MODERATE	IMPORTANT

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Mobilisation 8 hours after surgery												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	very serious[2]	none	11/60 (18.3%)	7/60 (11.7%)	RR 1.57 (0.65 to 3.78)	67 more per 1000 (from 41 fewer to 324 more)	⊕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] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.
[4] Outcome is 8 hours after surgery rather than 1 day

Table 22: Clinical evidence profile: regional anaesthesia versus general anaesthesia

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Regional anaesthesia**	**General anaesthesia**	**Relative (95% CI)**	**Absolute**		
Postoperative use of analgesia (measured with: Unclear follow-up time; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	35	-	MD 2.89 lower (4.27 to 1.51 lower)	⊕OOO VERY LOW	IMPORTANT
Length of stay (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	58	60	-	MD 4 higher (1.33 to 6.67 higher)	⊕OOO VERY LOW	IMPORTANT
Mobilisation within 24 hours after surgery (follow-up mean 12 hours)												

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1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57/58 (98.3%)	60/60 (100%)	RR 0.98 (0.94 to 1.03)	20 fewer per 1000 (from 60 fewer to 30 more)	⊕⊕⊕O MODERATE	IMPORTANT
Mortality within 30 days of surgery (follow-up 30 days)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none			OR 1.19 (0.57 to 2.53)		⊕OOO VERY LOW	CRITICAL
Mortality within 90 days of surgery (follow-up 30 days)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	Adjusted HR 0.85 (0.74 to 0.97)	-	⊕OOO VERY LOW	CRITICAL

[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.

Table 23: Clinical evidence profile: general anaesthesia with LIA versus general anaesthesia with nerve block

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**General anaesthesia with LIA versus general anaesthesia with nerve block**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life within 30 days via Quality of Recovery (follow-up mean 1 days; measured with: QoR-40; range of scores: 40-200; Better indicated by lower values)												

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1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50	49	-	MD 5.9 higher (1.05 to 10.75 higher)	⊕⊕⊕O MODERATE	
Postoperative use of analgesia (follow-up mean 1 days; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	49	-	MD 3.2 lower (15.42 lower to 9.02 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Length of stay (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	49	-	MD 0 higher (0.28 lower to 0.28 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 24: Clinical evidence profile: general anaesthesia with LIA 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 LIA versus general anaesthesia**	**Control**	**Relative (95% CI)**	**Absolute**		
Postoperative pain within 30 days (follow-up mean 4 hours after surgery; measured with: Visual Analogue Scale; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	75	75	-	MD 0.48 lower (0.97 lower to 0.01	⊕OOO VERY LOW	CRITICAL

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										higher)		
Postoperative neurocognitive decline within 30 days (follow-up mean 10 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/19 (0%)	0/16 (0%)	See comment[4]	0 fewer per 1000 (from 110 fewer to 110 more)[5]	⊕OOO VERY LOW	CRITICAL
Postoperative use of analgesia (follow-up mean 2 days; measured with: varying methods; Better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	139	137	-	MD 1.94 lower (6.2 lower to 2.33 higher)	⊕⊕⊕O MODERATE	CRITICAL
Number of people using postoperative NSAIDs (follow-up while admitted in hospital)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/29 (13.8%)	4/29 (13.8%)	RR 1 (0.28 to 3.62)	0 fewer per 1000 (from 99 fewer to 361 more)	⊕OOO VERY LOW	IMPORTANT
Length of stay (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	120	121	-	MD 0.1 lower (0.4 lower to 0.2 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Nausea within 30 days days (follow-up mean 4 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	21/74 (28.4%)	26/75 (34.7%)	RR 0.82 (0.51 to 1.32)	62 fewer per 1000 (from 170 fewer to 111 more)	⊕OOO VERY LOW	IMPORTANT

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Mobilisation within 24 hours after surgery												
1	randomised trials	very serious[1]	no serious inconsistency	serious[6]	no serious imprecision	none	3/29 (10.3%)	3/29 (10.3%)	RR 1 (0.22 to 4.55)	0 fewer per 1000 (from 81 fewer to 367 more)	⊕OOO VERY LOW	IMPORTANT
Time to mobilisation (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	75	75	-	MD 0.1 lower (0.4 lower to 0.2 higher)	⊕⊕⊕O MODERATE	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] Downgraded one increment for imprecision as it is a small study with no events.
[4] Comparative effect analysed using risk difference due to zero events in both treatment arms
[5] Absolute effect calculated using the risk difference
[6] Study outcome was walk in the corridor on postoperative day 2

Table 25: Clinical evidence profile: general anaesthesia with nerve block versus general anaesthesia

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General anaesthesia with nerve block versus general anaesthesia	Control	Relative (95% CI)	Absolute		
Postoperative pain within 30 days (follow-up mean 1 days; measured with: Visual Analogue Scale; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	26	-	MD 2.3 lower (3.42 to 1.18 lower)	⊕⊕OO LOW	CRITICAL
Postoperative use of analgesia (follow-up unclear; Better indicated by lower values)												

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1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	26	-	MD 223 lower (426.43 to 19.57 lower)	⊕OOO VERY LOW	CRITICAL

[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.

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Appendix G: Health economic evidence selection

Figure 35: Flow chart of health economic study selection for the guideline

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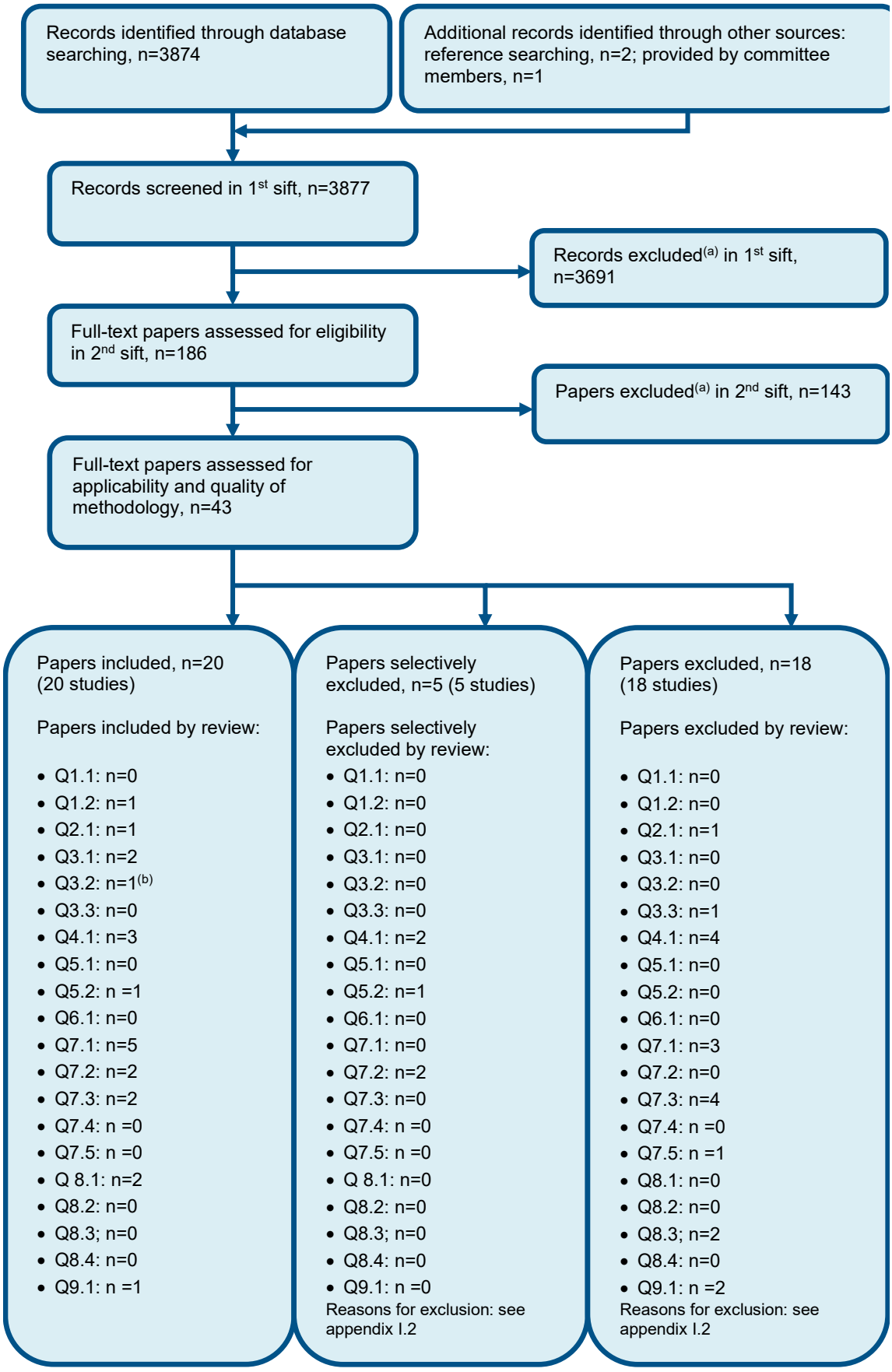

a) Non-relevant population, intervention, comparison, design or setting; non-English language
b) One study was applicable to both Q3.1 and Q3.2

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Appendix H: Health economic evidence tables

Study	Marques 2015[147]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Within-trial analysis (APEX trial) **Approach to analysis:** Analysis of the costs and outcomes of different anaesthetic regimens for people undergoing THR **Perspective:** UK NHS **Follow-up:** 12 months post operatively **Discounting:** Costs: N/A; Outcomes: N/A	**Population:** People who have undergone primary THR **Cohort characteristics:** n=322 Start age: NR Male: NR **Intervention 1:** Standard anaesthesia which consisted of a spinal anaesthetic alone or in combination with sedation/light general anaesthetic **Intervention 2:** Intra-operative LAI, administered before wound closure, in addition to the standard anaesthetic regimen	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): Intervention 2 saves £86 per person (95% CI: £-571 to £399; p=0.730) **Currency & cost year:** 2013 UK Pounds, also presented here as 2013 UK pounds **Cost components incorporated:** Operating theatre time, intra-operative LAI injection (for intervention group), time spent in recovery, number of days admitted to ward after surgery. After discharge costs included, accident and emergency visits, inpatient and outpatient visits. Secondary care, community based care, medication and social service use were recorded via questionnaire.	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1):0.052 (95% CI: 0.017 to 0.087; p=0.004) **Inpatient admissions after discharge (total):** Intervention 1: 122/159 (76.7%)[(a)] Intervention 2: 115/163 (70.6%) Incremental (2−1): 6.1%	Intervention 2 dominates Intervention 1 **Analysis of uncertainty:** One-way deterministic sensitivity analyses investigating 4 scenarios was conducted; using macro-costed prescribed medications, 50% higher local inpatient costs, 50% lower local inpatient costs and dropping anomalously high cost patients. Intervention 2 remained dominant in all instances. A probabilistic sensitivity analysis showed a probability of 98% that LAI was cost effective at a threshold of £20,000 per QALY gained.
Data sources				
Health outcomes: QALYs calculated from patient questionnaires filled out at 3, 6 and 12 months after surgery **Quality-of-life weights:** Trial participants filled out the EQ-5D-3L questionnaire. **Cost sources:** Resource use was estimated from medical records and patient logs and questionnaires. Unit costs for the initial hospital stay were obtained from the North Bristol Trust finance department. Unit costs for LAI injections were provided by the Management and Procurement Department at North Bristol NHS Trust. HRGs for secondary care visits were valued using 2012/13 NHS Reference Costs. Community-based costs were obtained from Curtis' unit costs for health and social care. Costs for prescribed medications were taken from the BNF.				
Comments				

Source of funding: National Institute for Health Research **Limitations:** Complete cost and QALY data was available for only 159/322 (49%) of participants. The final dataset therefore included imputed missing costs and outcome data. Outcomes from a single RCT rather than a systematic review	
Overall applicability:(b) Directly applicable	**Overall quality:**(c) Minor limitations

Abbreviations: BNF; British National Formulary; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HRGs; healthcare resource groups; ICER= incremental cost-effectiveness ratio; LAI: local anaesthetic wound infiltration; NR= not reported; QALYs= quality-adjusted life years; THR: total hip replacement.

(a) Figures from available cases before imputation for missing data
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Gonano 2006[88]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost comparison **Study design:** Within-trial RCT Gonano2006 [88] **Approach to analysis:** Recording of resource use and relevant unit costs for individuals randomised to 2 different methods of anaesthesia **Perspective:** Austrian hospital **Follow-up**: duration from the start of anaesthesia until transfer to a normal ward **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** People undergoing elective THR. **Cohort characteristics:** Intervention 1, n=12 Mean age: 61 (SD:9) Male: NR Intervention 2, n=10 Mean age: 64 (SD:10) Male: NR **Intervention 1:** General anaesthesia (induced by fentanyl and propofol) **Intervention 2:** Spinal anaesthesia (injection of bupivacaine)	**Total costs (mean per patient):** Intervention 1: £63.47 Intervention 2: £34.29 Incremental (2−1): £29.18 (95% CI: NR; p=NR) **Currency & cost year:** 2004 Euros, presented here as 2004 British pounds[(a)] **Cost components incorporated:** Anaesthesia supplies, drugs/gases used and recovery drugs/supplies used. Personnel costs were not included	**Pain at admission to PACU (VAS)[(b)]:** Intervention 1: 4.7 (SD: 4.0) Intervention 2: 0.4 (SD:1.2) Incremental (2−1): 4.3	Intervention 2 is cost saving over Intervention 1 **Analysis of uncertainty:** Four scenario analyses were conducted. These explored varying the use of muscle relaxants, fresh gas flow, and use of isoflurane instead of sevoflurane. Spinal anaesthesia being cost saving was robust to all these analyses.
Data sources				
Health outcomes: Both interventions showed comparable times for anaesthesia, surgery and recovery. Pain was recorded at admission to PACU using the VAS score. **Quality-of-life weights:** Pain VAS was used but not in order to calculate QALYs. **Cost sources:** Resource use of patients recorded during the trial. Unit cost source is unclear but they are likely to be from the hospital.				
Comments				

Source of funding: NR. **Limitations:** No QALYs or other health outcomes are used to conduct a cost effectiveness analysis. Personnel costs are not included. The overall study population included both TKR and THR procedures; the results presented are from the THR sub-group so the sample size is reduced. Very short time horizon.

Overall applicability:(c) Partially applicable **Overall quality:**(d) Potentially serious limitations

Abbreviations: NR= not reported; PACU= post-anaesthesia care unit; QALYs= quality-adjusted life years; TKR: Total knee replacement; THR: total hip replacement; VAS: visual analogue scale

(a) Converted using 2004 purchasing power parities[180]

(b) VAS pain score goes from: 0 = no pain at all to 10 = the worst pain imaginable

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

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 26) 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[168] 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 8 hours on average for hip 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 duration of effect 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 if it is considered that nerve blocks have an effect upon longer 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 26 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 26: 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)[47]; CG124[168]

(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[168]

I.2 Results

The gain in QALY and gain in HRQoL needed under a range of different scenarios is shown in Table 27. For a number of scenarios; particularly when the time to administer was 30 minutes, the duration of 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 27: 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.

The committee agreed that there is clinical benefit to the addition of nerve blocks, although they are only likely to be cost effective when administered by an experienced anaesthetist (leading to reduced administration time), theatre time is not included (so two anaesthetists are present) and the duration of effect is longer (as discussed, the most appropriate duration of effect is arguable). The circumstances when nerve blocks are cost effective may be found in some hospitals but not in others. Therefore the committee decided on a recommendation to consider a nerve block as an alternative to LIA.

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 28: Studies excluded from the clinical review

Study	Exclusion reason
Affas 2016[1]	Unclear if the study population is people undergoing primary arthroplasty
Aguirre 2012[2]	Unclear if the study population is people undergoing primary hip arthroplasty
Ahmed 2017[3]	Not review population
Aksoy 2014[4]	Unclear if the study population is people undergoing primary arthroplasty
Andersen 2007[6]	Unclear if the study population is people undergoing primary hip arthroplasty
Andersen 2007[7]	Unclear if the study population is people undergoing primary arthroplasty
Andersen 2011[9]	Unclear if the study population is people undergoing primary hip arthroplasty
Andersen 2014[8]	Systematic review with different inclusion criteria however included studies were checked for this review
Andersen 2015[5]	Incorrect interventions
Anonymous 2018[10]	Correction of excluded paper
Asajima 1998[11]	Not in English
Atchabahian 2015[12]	Systematic review with different inclusion criteria however included studies were checked for this review
Axelsson 2005[13]	Unclear if the study population is people undergoing primary arthroplasty
Babaiants 2008[14]	Not in English
Bakalov 2016[15]	Unable to obtain
Bang 2016[16]	Unclear if the study population is people undergoing primary hip arthroplasty
Banwait 2012[17]	Unclear if the study population is people undergoing primary arthroplasty
Becchi 2008[19]	Incorrect interventions
Bertini 1995[21]	Not in English
Bertini 2001[20]	Unclear if the study population is people undergoing primary arthroplasty
Bianconi 2003[22]	Not review population
Biboulet 2004[23]	Unclear if the study population is people undergoing primary arthroplasty
Bichel 1998[24]	Not in English
Bogoch 2002[25]	Not review population
Borghi 2002[26]	Unclear if the study population is people undergoing primary hip arthroplasty
Borghi 2002[28]	Not in English
Borghi 2005[27]	Unclear if the study population is people undergoing primary hip arthroplasty
Borisov 2012[29]	Not in English

Study	Exclusion reason
Brinker 1997[30]	Incorrect study design
Brueckner 1997[32]	Conference abstract
Brueckner 2003[31]	Incorrect study design
Burton 2019[33]	Unclear if the study population is people undergoing primary hip arthroplasty
Busch 2010[34]	Unclear if the study population is people undergoing primary hip arthroplasty
Carpintero Benítez 1986[35]	Not in English
Casati 2003[36]	Not review population
Celidonio 2008[37]	Unable to obtain
Chen 1998[43]	Not in English
Chen 2015[41]	Not in English
Chen 2015[42]	Included people having revision joint replacement surgery
Chen 2017[39]	Not review population
ChiCTR 2017[44]	Conference abstract
Chu 2015[45]	Not review population
Chudinov 1999[46]	Not review population
Dahn 1999[49]	Not in English
Dahn 2003[48]	Not in English
Dauphin 1997[50]	Unclear if the study population is people undergoing primary hip arthroplasty
Davis 1987[53]	Unclear if the study population is people undergoing primary hip arthroplasty
Davis 1987[54]	Unclear if the study population is people undergoing primary hip arthroplasty
Davis 1989[51]	Unclear if the study population is people undergoing primary hip arthroplasty
Davis 1989[52]	Unclear if the study population is people undergoing primary hip arthroplasty
Demirel 2014[55]	Unclear if the study population is people undergoing primary hip arthroplasty
Deng C 2015[57]	Not in English
Deniz 2014[58]	Unclear if the study population is people undergoing primary hip arthroplasty
Desmet 2017[59]	Unclear if the study population is people undergoing primary hip arthroplasty
Divella 2012[60]	Unclear if the study population is people undergoing primary hip arthroplasty
Drakeford 1991[63]	Unclear if the study population is people undergoing primary hip arthroplasty
Duarte 2009[65]	Inappropriate comparison
Essving 2011[67]	Unclear if the study population is people undergoing primary arthroplasty
Etches 1995[68]	Inappropriate comparison
Fields 2015[70]	Not review population
Fletcher 1995[71]	Inappropriate comparison
Fogarty 1995[72]	Unclear if the study population is people undergoing primary hip arthroplasty
Forget 2009[73]	Not in English

Study	Exclusion reason
Forst 1999[74]	Incorrect interventions
Foss 2005[75]	Not review population
Fouad 2010[76]	Conference abstract
Fournier 1996[77]	Conference abstract
Fournier 1996[78]	Conference abstract
Fournier 1998[79]	Unclear if the study population is people undergoing primary hip arthroplasty
Fournier 2005[80]	Incorrect interventions
Frassanito 2008[81]	Inappropriate comparison
Fredin 1986[82]	Unclear if the study population is people undergoing primary arthroplasty
Fredrickson 2015[83]	Incorrect interventions
Gasanova 2019[84]	Unclear if the study population is people undergoing primary hip arthroplasty
Gelmanas 2010[85]	Conference abstract
Ghabach 2016[86]	Unclear if the study population is people undergoing primary hip arthroplasty
Ghoneim 1988[87]	Not review population
Gonano 2006[88]	Not review population
Greimel 2017[92]	Observational study without adjustment for confounding factors
Guay 2014[93]	Overview of Cochrane reviews
Guay 2017[94]	Systematic review with different inclusion criteria however included studies were checked for this review
Haghighi 2017[95]	Unclear if the study population is people undergoing primary hip arthroplasty
Heidari 2011[98]	Not review population
Helwani 2015[99]	Included people having revision joint replacement surgery
Hemmerling 2010[100]	Unclear if the study population is people undergoing primary arthroplasty
Hole 1980[103]	Unclear if the study population is people undergoing primary hip arthroplasty
Hua 2017[104]	Unclear if the study population is people undergoing primary hip arthroplasty
Ilango 2016[106]	Incorrect study design
Ilfeld 2009[107]	Incorrect interventions
Ilfeld 2010[108]	Incorrect interventions
Jakobsen 1986[109]	Unclear if the study population is people undergoing primary hip arthroplasty
Jia 2017[110]	Systematic review with different inclusion criteria however included studies were checked for this review
Jimenez-almonte 2016[111]	Systematic review with different inclusion criteria however included studies were checked for this review
Johnson 2016[113]	Systematic review with different inclusion criteria however included studies were checked for this review
Johnson 2017[112]	Incorrect interventions
Jones 1990[114]	Unclear if the study population is people undergoing primary hip arthroplasty
Juelsgaard 1998[115]	Not review population
Jules-elysee 2015[116]	Inappropriate comparison

Study	Exclusion reason
Kacha 2018[117]	Not review population
Kai 2010[118]	Not in English
Kampe 1999[121]	Unclear if the study population is people undergoing primary arthroplasty
Kampe 2001[120]	Unclear if the study population is people undergoing primary arthroplasty
Kampe 2003[119]	Unclear if the study population is people undergoing primary arthroplasty
Kandler 1993[122]	Incorrect interventions
Karaaslan 2006[123]	Not in English
Kaya 2006[124]	Not in English
Kearns 2016[125]	Inappropriate comparison
Kehlet 2015[126]	Literature review
Kendrisic 2017[127]	Unclear if the study population is people undergoing primary hip arthroplasty
Kim 2002[129]	Not in English
Kim 2007[128]	Not in English
Koehler 2017[130]	Incorrect interventions
Koroglu 2008[131]	Unclear if the study population is people undergoing primary arthroplasty
Kuchalik 2013[133]	Not in English
Kuchalik 2017[135]	Inappropriate comparison
Kuchalik 2017[136]	Unclear if the study population is people undergoing primary hip arthroplasty
Lee 2009[137]	Incorrect interventions
Li 2018[138]	Not in English
Liu 2014[139]	Incorrect study design
Loncar Stojiljkovic 2016[141]	Unclear if the study population is people undergoing primary arthroplasty
Lu 2010[142]	Not in English
Mandal 2011[144]	Unclear if the study population is people undergoing primary hip arthroplasty
Marino 2009[145]	Inappropriate comparison
Markel 1997[146]	Unclear if the study population is people undergoing primary arthroplasty
Marshall 2008[148]	Unable to obtain
Martin 2006[149]	People undergoing revision surgery included in the study
Maurer 2003[150]	Unclear if the study population is people undergoing primary arthroplasty
Mcbeath 1995[152]	Observational study with no adjustment for confounding factors
Mcgraw-tatum 2017[153]	Unclear if the study population is people undergoing primary hip arthroplasty
Mei 2017[154]	Unclear if the study population is people undergoing primary hip arthroplasty
Mendieta sánchez 1999[155]	Not in English
Messina 2013[156]	Not review population
Meuret 2018[157]	Not review population
Modig 1976[158]	Observational study with no adjustment for confounding factors

Study	Exclusion reason
Modig 1981[161]	Unclear if the study population is people undergoing primary hip arthroplasty
Modig 1983[159]	Unclear if the study population is people undergoing primary hip arthroplasty
Modig 1983[160]	Unclear if the study population is people undergoing primary hip arthroplasty
Mouzopoulos 2009[163]	Not review population
Murphy 1984[164]	Inappropriate comparison
Nakai 2013[166]	Unclear if the study population is people undergoing primary arthroplasty
Neuman 2016[169]	Study protocol
Neuman 2016[170]	Unclear if the study population is people undergoing primary hip arthroplasty
Nielsen 2019[172]	Incorrect interventions
Niemi 1993[174]	Included people having revision joint replacement surgery
Niemi 1996[173]	Not review population
Nishi 2018[175]	Not review population
Nishio 2014[177]	Incorrect interventions
Nishio 2017[176]	Unclear if the study population is people undergoing primary arthroplasty
Nohel 2011[178]	Conference abstract
Onal 2007[179]	Not in English
Ozhan 2012[181]	Not in English
Pandazi 2013[182]	Unclear if the study population is people undergoing primary hip arthroplasty
Park 1994[183]	Not in English
Parker 2015[184]	Not review population
Parvataneni 2007[185]	Inappropriate comparison
Patorno 2014[186]	Not review population
Pavy 2007[187]	Not in English
Pedersen 1986[188]	Not in English
Perlas 2016[189]	Not review population
Racle 1986[190]	Not in English
Rashid 2013[191]	Not review population
Riis 1983[192]	Unclear if the study population is people undergoing primary hip arthroplasty
Rikalainen-salmi 2012[193]	Unclear if the study population is people undergoing primary hip arthroplasty
Saglik 2015[194]	Unclear if the study population is people undergoing primary hip arthroplasty
Saksena Shrivastava 2011[195]	Conference abstract
Salo 1990[196]	Unclear if the study population is people undergoing primary hip arthroplasty
Sansonnens 2016[197]	Incorrect study design
Seet 2006[198]	Not review population
Shariat 2013[199]	Unclear if the study population is people undergoing primary arthroplasty
Shi 2015[200]	Observational study without adjustment for confounding factors

Study	Exclusion reason
Siddiqui 2007[201]	Unclear if the study population is people undergoing primary hip arthroplasty
Singelyn 1999[203]	Unclear if the study population is people undergoing primary arthroplasty
Singelyn 2005[202]	Unclear if the study population is people undergoing primary arthroplasty
Sitsen 2007[204]	Not review population
Smet 2008[205]	Not review population
Solovyova 2013[206]	Unclear if the study population is people undergoing primary arthroplasty
Souron 2003[207]	Incorrect interventions
Specht 2011[208]	Inappropriate comparison
Srampickal 2019[209]	Incorrect interventions
Stevens 2000[211]	Unclear if the study population is people undergoing primary hip arthroplasty
Stevens 2007[210]	Unclear if the study population is people undergoing primary arthroplasty
Striebel 1993[212]	Not in English
Stundner 2012[213]	Not review population
Sun 2014[214]	Not in English
Surange 2012[215]	Unclear if the study population is people undergoing primary hip arthroplasty
Sveticic 2004[216]	Not review population
Tammachote 2013[217]	Not review population
Tetsunaga 2015[218]	Observational study with no adjustment for confounding factors
Thomas 2009[219]	Conference abstract
Thybo 2016[220]	Incorrect interventions
Thybo 2016[221]	Incorrect interventions
Turker 2003[223]	Unclear if the study population is people undergoing primary arthroplasty
Tzimas 2018[225]	Not review population
Uhrbrand 1992[226]	Unclear if the study population is people undergoing primary hip arthroplasty
Valentin 1986[227]	Unclear if the study population is people undergoing primary hip arthroplasty
Van herreweghe 2015[228]	Conference abstract
Vermeylen 2019[229]	Not in English
Wang 2006[231]	Not in English
Wang 2017[232]	Systematic review with different inclusion criteria however included studies were checked for this review
Whiting 2015[233]	Not review population
Wiesmann 2014[234]	Unclear if the study population is people undergoing primary hip arthroplasty
Wulf 1999[235]	Unclear if the study population is people undergoing primary hip arthroplasty
Yhim 2017[237]	Unclear if the study population is people undergoing primary hip arthroplasty
Zorrilla-vaca 2016[239]	Systematic review with different inclusion criteria however included studies were checked for this review

J.2 Excluded health economic studies

Studies that meet the review protocol population and interventions, and the economic study inclusion criteria but have not been included in the review based on applicability and/or methodological quality are summarised below with reasons for exclusion.

Table 29: Studies excluded from the health economic review

Reference	Reason for exclusion
None	