National Institute for Health and Care Excellence

Draft for consultation

Joint replacement (primary): hip, knee and shoulder

[E] Evidence review on anaesthesia for knee replacement

NICE guideline

Intervention evidence review

October 2019

Draft for Consultation

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

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ISBN

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1.1 Review question: In adults having primary elective knee joint replacement, what is the clinical and cost effectiveness of 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 knee replacement surgery is painful. The anaesthetist and person undergoing surgery can choose from a number of interventions to prevent 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 – a nerve block. For the knee, this would typically be an injection of local anaesthetic into the fluid that surrounds the spine (a spinal anaesthetic) to numb both legs. 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 it 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 knee 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 knee 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)

	• 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 knee joint replacement surgery.

Thirty-eight RCTs were included in the review;[15, 17, 29, 37, 43, 51, 55, 86, 89, 95, 98, 104, 134, 135, 139, 176, 181, 185, 186, 201, 225, 227, 230, 232, 236, 244, 267, 273, 292-294, 300, 305, 307, 309-311, 317, 320] these are summarised in Table 2 below. The table has been divided into the 15 comparisons found in the evidence and studies with multiple comparisons feature multiple times. 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.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included each comparison in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Regional anaesthesia versus general anaesthesia				
Mitchell 1991[185]	One group had regional via epidural anaesthesia. The other group had general anaesthesia where sodium thiopental was used for induction.	Adults with osteoarthritis or rheumatoid arthritis who are scheduled for primary TKA. Mean (range) age: 64 (38-84) ASA: not stated N=72	• Thromboembolic complications	USA
Williams-Russo 1995[309, 310]	One group had regional via epidural anaesthesia using lidocaine or bupivacaine. The other group had general anaesthesia induced with thiopental sodium, fentanyl and vecuronium. Maintenance with fentanyl and nitrous oxide.	People over 40 years old undergoing elective unilateral TKA Median age: 69 ASA: Not stated N=262	• Mortality • Postoperative neurocognitive decline • Thromboembolic complications • Length of stay • Mobilisation: time until transfer unassisted	USA
Regional anaesthesia versus general anaesthesia with nerve block				
Kayupov 2018[135]	One group had regional via combined spinal/epidural anaesthesia. The other group had general anaesthesia and continuous adductor canal block (CACB).	People with osteoarthritis who are scheduled to undergo primary unilateral TKA Mean age: 64, 63, 60 ASA: not stated N=99	• Postoperative pain • Length of stay • Mobilisation: ambulating distance on postoperative day 1	USA
Regional anaesthesia with LIA versus general anaesthesia with LIA				
Harsten 2013[98]	One group had regional via spinal anaesthesia using bupivacaine. The other group	People between 45 and 85 years of age with osteoarthritis undergoing	• Thromboembolic complications • Length of stay	Sweden

Study	Intervention and comparison	Population	Outcomes	Comments
	had general anaesthesia via target controlled infusion (TCI) with propofol and remifentanil. Towards the end of surgery, all subjects received infiltration of local anaesthetic (epinephrine and ropivacaine) in the perisurgical area.	TKA. Mean (SD) age: 68 (7) and 67 (7) ASA: I-III N=120	• Nausea • Mobilisation within 24 hours after surgery	
Regional anaesthesia with nerve block versus general anaesthesia with nerve block				
Kayupov 2018[135]	One group had regional via spinal anaesthesia. The other group had general anaesthesia. All people had a continuous adductor canal block (CACB).	People with osteoarthritis who are scheduled to undergo primary unilateral TKA Mean age: 64, 63, 60 ASA: not stated N=94	• Postoperative pain • Length of stay • Mobilisation: ambulating distance on postoperative day 1	USA
General and regional anaesthesia versus general anaesthesia and nerve block				
Davies 2004[51]	All people had general anaesthesia induced with propofol and fentanyl. One group had epidural anaesthesia using bupivacaine. commenced after surgical incision. The other group had combined femoral (3-in-1) and sciatic nerve block.	Adults undergoing unilateral primary total knee replacement Mean (SD) age: 73 (9) and 72 (10) ASA: I-III N=60	• Postoperative pain	UK
Sakai 2013[236]	All people had general anaesthesia induced with propofol. One group had continuous femoral nerve block using ropivacaine. The other group had regional via epidural anaesthesia using ropivacaine.	Adults who are scheduled for primary unilateral TKA Median (range) age: 73 (53-86) and 72 (48-84) ASA: I-III N=66	• Nausea • Mobilisation within 24 hours after surgery	Japan

Study	Intervention and comparison	Population	Outcomes	Comments
Regional anaesthesia with LIA versus regional anaesthesia				
Dimaculangan 2019[55]	All people had spinal anaesthesia using bupivacaine. One group had LIA using ropivacaine, epinephrine, ketorlac, morphine, and saline. The other group had sham LIA.	Adults with primary osteoarthritis who are scheduled for elective unilateral primary TKA Mean (SD) age: 65 (8) and 62 (11) ASA: II-III N=44	• Postoperative pain • Postoperative use of analgesia • Length of stay	USA
Goyal 2013[86]	All people had regional via spinal anaesthesia with bupivacaine. One group had LIA immediately after the operation using bupivacaine and the other received sham LIA.	Adults undergoing primary, unilateral TKA for degenerative arthritis. Mean age: 63 and 65 ASA: I-III N=160	• Postoperative pain • Thromboembolic complications • Hospital readmissions • Postoperative use of analgesia	USA
Han 2007[95]	All people had regional via spinal anaesthesia using tetracaine. One group had LIA using ropivacaine, epinephrine and morphine injected into 10 different areas around the synovium.	People scheduled for primary TKA Mean (range) age: 69 (58-78), 68 (52-79), 67 (52-78) ASA: I-II N=90	• Postoperative pain • Postoperative use of analgesia • Nausea	South Korea There were 2 regional with LIA treatment groups.
Hinarejos 2016[104]	All people had regional via spinal anaesthesia using bupivacaine. One group had LIA using ropivacaine, epinephrine, and ketorolac in the soft tissues around the join before closure.	People with knee osteoarthritis who are 40-85 years old and scheduled for TKA Mean (SD) age: 72 (7) ASA: not stated N=101	• Thromboembolic complications • Hospital readmissions • Postoperative use of analgesia: use of rescue medication	Spain
Milani 2015[181]	All people had regional via single shot spinal anaesthesia using bupivacaine. One group had LIA via periarticular	Adults over 60 years of age, with primary knee osteoarthritis, who are scheduled for primary	No outcomes	Italy

Study	Intervention and comparison	Population	Outcomes	Comments
	ropivacaine administered before wound closure. The other had sham LIA using saline.	unilateral TKA. Mean (SD) age: 71 (8). N=64		
Niemelainen 2014[201]	Everyone had single shot anaesthesia induced using bupivacaine. One group had intraoperative LIA at 2 stages with a solution containing levobupivacaine, ketorolac and adrenaline. The other group had placebo LIA.	People aged 18–75 years with osteoarthritis undergoing unilateral primary TKA Mean (SD) age: 65 (5) and 64 (7) ASA: I-III N=60	• Postoperative pain: removed from study • Postoperative use of analgesia • Nausea	Finland
Vaishya 2015[294]	All people had regional via spinal anaesthesia using bupivacaine heavy with preservative free fentanyl. One group had LIA at 3 points during surgery using bupivacaine, morphine, ketorolac, adrenaline, gentamycin, and saline. The other group had LIA placebo.	People scheduled for unilateral primary TKA Mean (SD) age: 64 (10) and 65 (9) ASA: I-III N=100	• Postoperative pain • Length of stay • Nausea	India
Williams 2013[311]	All people had regional via spinal anaesthetic using bupivacaine and fentanyl. One group had continuous LIA via a catheter using bupivacaine for 48 hours after the surgery. The other group had LIA placebo.	Adults 18-90 years old with osteoarthritis who are scheduled to undergo primary unilateral TKA Mean (SD) age: 66 (10) and 67 (13) ASA: I-IV N=67	• Postoperative pain • Postoperative use of analgesia • Length of stay • Nausea	Canada
Regional anaesthesia with nerve block versus regional anaesthesia				
Chan 2014[36]	Everyone had spinal anaesthesia with hyperbaric bupivacaine. One group had a	People scheduled for unilateral, primary TKA. Age: 68 (9) and 71 (9)	• Postoperative pain • Postoperative use of analgesia	Taiwan

Study	Intervention and comparison	Population	Outcomes	Comments
	femoral nerve block using bupivacaine and epinephrine. The other group had a sham block.	ASA: I-III N=40	• Nausea	
Kayupov 2018[135]	One group had regional via spinal anaesthesia and continuous adductor canal block (CACB). The other had regional via combined spinal/epidural anaesthesia.	People with osteoarthritis who are scheduled to undergo primary unilateral TKA Mean age: 64, 63, 60 ASA: not stated N=97	• Postoperative pain • Length of stay • Mobilisation: ambulation distance on Postoperative day 1	USA
McNamee 2001[176]	Everyone had regional via spinal anaesthesia using bupivacaine. One group had femoral and sciatic nerve blocks using bupivacaine. The other group had sham blocks.	Adults scheduled to undergo primary unilateral TKA. Mean (range) age: 70 (54-84), 69 (58-83), 68 (47-83) ASA: I-III N=75	No outcomes	UK
YaDeau 2005[317]	Everyone had regional via combined spinal epidural anaesthesia using bupivacaine. One group had femoral nerve block using bupivacaine and epinephrine whilst the other one had a placebo.	People under 85 years old with osteoarthritis scheduled for primary TKA Mean (SD) age: 72 (8) and 73 (8) ASA: not stated N=80	• Postoperative pain (VAS >/= 6) • Nausea	USA
Regional anaesthesia with local infiltration analgesia (LIA) versus regional anaesthesia with nerve block				
Ashraf 2013[16]	All people had regional via spinal anaesthesia using bupivacaine. The LIA group used ropivacaine, adrenaline and ketorolac into all layers of the knee joint. The nerve block group had single shot ultrasound guided femoral nerve block using ropivacaine.	People scheduled to undergo primary TKR Unclear age or ASA N=42	• Postoperative pain • Postoperative use of analgesia • Length of stay	UK

Study	Intervention and comparison	Population	Outcomes	Comments
Choi 2016[43]	All people had regional via spinal anaesthesia using bupivacauine and fentanyl. One group given intraoperative LIA using ropivacaine, epinephrine, and ketorolac and a sham femoral nerve block. The other received a single injection femoral nerve block using ropivacaine and sham LIA using saline.	Adults 85 years old or younger scheduled to undergo primary tricompartmental TKA ASA: I-III Mean (SD) age: 64 (7), 65 (9), 66 (8) N=80	• Postoperative pain • Postoperative use of analgesia	Canada
Grosso 2018[89]	All people had regional via spinal anaesthesia. One group had LIA performed intraoperatively using bupivacaine at two points during surgery. The other received a adductor canal block (ACB) using bupivacaine.	People undergoing elective unilateral primary TKA Mean age: 69, 73, 71 ASA: not stated N=99	• Postoperative pain • Postoperative use of analgesia • Length of stay	USA
Moghtadaei 2014[186]	All people had regional via spinal anesthesia using bupivacaine hydrochloride. One group received LIA using ropivacaine, ketorolac, and epinephrine in 3 syringes utilised at 3 points during surgery. The other group had femoral nerve block using ropivacaine.	People with osteoarthritis, aged 20 to 85 years old, who are scheduled for TKA. Mean (SD) age: 67 (7) and 64 (7) ASA: I-III N=40	• Hospital readmissions • Nausea	Iran
Runge 2016[230]	All people had regional via spinal anaesthesia using bupivacaine. One group had Intraoperative LIA using ropivacaine, epinephrine, and ketorolac and the other received sham LIA. One group	Adults over 50 years of age, undergoing cemented unilateral primary TKA Mean (SD) age: 71 (8), 73 (7), 70 (8) ASA: I-III	No outcomes	Denmark There were 2 regional anaesthesia with nerve block groups

Study	Intervention and comparison	Population	Outcomes	Comments
	received femoral triangle block and obturator nerve block using bupivacaine, epinephrine, clonidine, and dexamethasone. The other group had sham blocks.	N=78		
Sawhney 2016[244]	All people had regional via spinal anaesthesia using bupivacaine. One group had LIA at 3 points during surgery during surgery using ropivacaine, morphine, ketorolac, and saline. The other group had an AC block using ropivacaine. Sham LIA and blocks also utilised.	Adults who are scheduled for primary TKA. Mean (SD) age: 67 (10) ASA: I-III N=105	• Postoperative pain • Postoperative use of analgesia	Canada
Sogbein 2017[267]	All people had regional via spinal anaesthesia using hyperbaric bupivacaine. One group had LIA at 3 points during using ropivacaine, epinephrine, morphine, and ketorolac. The other group had a motor sparing block using ropivacaine, epinephrine, morphine and ketorolac. This involved a adductor canal block (ACB), posterior pericapsular injection, and lateral femoral cutaneous nerve block. Sham LIA and nerve blocks utilised.	People 18 to 85 years old who are scheduled for elective primary TKA. Mean (SD) age: 68 (8) and 63 (9) ASA: I-III N=82	• Thromboembolic complications • Postoperative use of analgesia • Length of stay	Canada
Uesugi 2014[293]	All people had regional via spinal anaesthesia using bupivacaine. One group had LIA at 2 points during surgery using ropivacaine, adrenaline,	People with osteoarthritis of the knee who were scheduled to undergo TKA. Mean (SD) age: 76 (6) and 76 (7)	• Postoperative pain: time to onset • Postoperative use of analgesia	Japan

Study	Intervention and comparison	Population	Outcomes	Comments
	morphine hydrochloride, dexamethasone and saline. The other group had femoral and sciatic nerve block using ropivacaine.	ASA: I-II N=210	• Nausea	
Regional anaesthesia with nerve block and LIA versus regional anaesthesia with LIA				
Biswas 2018[29]	All people had regional via spinal anaesthesia using bupivacaine and intraoperative LIA through ropivacaine, ketorolac and epinephrine. The nerve block group had an adductor canal block (ACB) while the other group had a sham ACB.	Adults capable of ambulating independently and ASA I-III undergoing elective unilateral TKA. Age (SD): 64 (8), 64 (8), 65 (9) N=134	• Postoperative pain requiring rescue IV PCA • Postoperative use of analgesia • Nausea	Canada
Grosso 2018[89]	All people had regional via spinal anaesthesia and LIA performed intraoperatively using bupivacaine at two points during surgery. One group had an adductor canal block (ACB) using bupivacaine.	People undergoing elective unilateral primary TKA Mean age: 69, 73, 71 ASA: not stated N=99	• Postoperative pain • Postoperative use of analgesia • Length of stay	USA
Kim 2018[139]	All people had regional via combined spinal epidural anaesthetic using mepivacaine and LIA using bupivacaine, epinephrine, methylprednisoline, cefazolin, and saline. This was injected at 2 times during the surgery. One group also had ACB and IPACK blocks using bupivacaine.	Adults with osteoarthritis who are scheduled for primary unilateral TKA Mean (SD) age: 67 (8) and 68 (7) ASA: I-III N=86	• Postoperative pain • Postoperative use of analgesia • Mobilisation: distance walked on postoperative day 1	USA
Sawhney 2016[244]	All people had regional via spinal anaesthesia using	Adults who are scheduled for primary TKA.	• Postoperative pain • Postoperative use of	Canada

Study	Intervention and comparison	Population	Outcomes	Comments
	bupivacaine and LIA at 3 points during surgery during surgery using ropivacaine, morphine, ketorolac, and saline. One group had AC block using ropivacaine. The other group had a sham nerve block.	Mean (SD) age: 67 (10) ASA: I-III N=108	analgesia	
Regional anaesthesia with nerve block and LIA versus regional anaesthesia with nerve block				
Grosso 2018[89]	All people had regional via spinal anaesthesia and an adductor canal block (ACB) using bupivacaine. One group received LIA performed intraoperatively using bupivacaine at two points during surgery.	People undergoing elective unilateral primary TKA Mean age: 69, 73, 71 ASA: not stated N=99	• Postoperative pain • Postoperative use of analgesia • Length of stay	USA
Safa 2014[232]	All people had regional via spinal anaesthesia using hypobaric bupivacaine. One group had LIA using ropivacaine utilised at the end of the surgical procedure. The other group had femoral nerve block using ropivacaine. LIA nerve block and LIA placebos were used.	Adults 18-75 years old who are scheduled for unilateral primary TKA Mean age: 61 ASA: I-III N=67	• Length of stay	Canada
Sawhney 2016[244]	All people had regional via spinal anaesthesia using bupivacaine and AC block using ropivacaine. One group had LIA at 3 points during surgery during surgery using ropivacaine, morphine, ketorolac, and saline. The other group had sham LIA.	Adults who are scheduled for primary TKA. Mean (SD) age: 67 (10) ASA: I-III N=105	• Postoperative pain • Postoperative use of analgesia	Canada

Study	Intervention and comparison	Population	Outcomes	Comments
Tziona 2018[292]	All people had regional via spinal anaesthesia using ropivacaine and an ultrasound guided ACB using ropivacaine and dexamethasone. One group had LIA using ropivacaine, adrenaline, and saline injected twice during surgery. The other group had placebo LIA.	Adults who are scheduled for primary unilateral cemented TKA Mean (SD) age: 73 (7) and 72 (9) ASA: I-III N=40	• Postoperative pain • Postoperative use of analgesia • Nausea	Greece
Watson 2005[305]	All people had regional via spinal anaesthesia using bupivacaine and lumbar plexus block and sciatic nerve block using levobupivacaine. One group had LIA using levobupivacaine infused into the plexus block catheter postoperatively. LIA placebo used in the other group.	Adults with osteoarthritis scheduled for primary unilateral bicompartmental cemented TKA. Mean (SD) age: 69 (7) and 72 (7) ASA: I-III N=32	• Mobilisation within 24 hours after surgery	UK
General anaesthesia with LIA versus general anaesthesia				
Rosen 2010[227]	All people had general anaesthesia. One group had LIA using ropivacaine injected into the intraarticular capsule after closure. The other group had a LIA placebo.	Adults scheduled to have unilateral elective primary TKA. Mean age: 71 ASA: not stated N=48	• Thromboembolic complications • Length of stay • Nausea	USA
General anaesthesia with nerve block versus general anaesthesia				
Stav 2017[273]	All people had general anaesthesia vi total intravenous anaesthesia with propofol and remifentanil. One group had a single injection femoral nerve block using bupivacaine. A second nerve block group had	Adults with osteoarthritis who are scheduled to undergo elective TKA Mean (SD) age: 69 (7), 69 (9), 67 (7) ASA: I-III	• Postoperative pain • Postoperative use of analgesia	Israel

Study	Intervention and comparison	Population	Outcomes	Comments
	multiple blocks on femoral, sciatic, obturator, and lateral femoral cutaneous nerves. A third group did not have a nerve block.	N=107		
General anaesthesia with LIA versus general anaesthesia with nerve block				
Kastelik 2019[134]	All people had general anaesthesia maintained with propofol or sevoflurane and bolus doses of fentanyl or continuous administration of remifentanil. One group had a single shot sciatic nerve block using ropivacaine and adductor canal block using prilocaine. The other group had periarticular infiltration with ropivacaine around knee joint capsule including the posterior joint structures, periarticular soft tissue and subcutaneous soft tissue.	Adults undergoing elective, primary TKA under general anaesthesia Mean (SD) age: 67 (10) ASA: I-III N=40	• Length of stay • Mobilisation	Germany
Rizk 2017[225]	All people had general anaesthesia. One group had LIA via Intraarticular and periarticular injections using ropivacaine, ketorolac, epinephrine, and morphine. The other group had adductor canal block (ACB) and sciatic nerve block (SNB) using ropivacaine.	People with primary osteoarthritis scheduled for unilateral primary TKA Mean (SD) age: 67 (7) and 69 (7) ASA: not stated N=75	• Postoperative use of analgesia • Length of stay • Mobilisation within 24 hours after surgery	Egypt
Youm 2016[320]	All people had general anaesthesia. One group had LIA before fixation of the implants using ropivacaine,	People 80 years old or younger with osteoarthritis who are scheduled to have unilateral TKA.	No outcomes	South Korea

Study	Intervention and comparison	Population	Outcomes	Comments
	morphine, epinephrine, methylprednisoline, ketorolac, cefoxitin, and saline. The other group had femoral nerve block using ropivacaine.	Mean age: 68, 70, 68 ASA: not stated N=60		
General anaesthesia with nerve block and LIA versus general anaesthesia with LIA				
Wallace 2012[300]	Everyone had general anaesthesia and peri-articular LIA using levobupivacaine, morphine, ketorolac, adrenaline, and saline. One group alos had femoral nerve block using levobupivacaine.	People undergoing primary unilateral TKR Median (IQR) age: 63.5 (61-74) and 63.5 (55.5-65) ASA: not stated N=46	No outcomes	UK
Widmer 2012[307]	Evereyone had general anaesthesia using propofol and maintained with sevoflurane. They also had LIA during the surgery using ropivacaine and adrenaline. One group had a preoperative femoral nerve block using ropivacaine. Sham nerve block used in the other group.	Adults scheduled for unilateral primary TKA Median (IQR) age: 72 (64-77) and 69 (63-76) ASA: not stated N=55	• Postoperative pain • Thromboembolic complications • Postoperative use of analgesia	Australia
Youm 2016[320]	All people had general anaesthesia and LIA before fixation of the implants using ropivacaine, morphine, epinephrine, methylprednisoline, ketorolac, cefoxitin, and saline. One group had femoral nerve block using ropivacaine	People 80 years old or younger with osteoarthritis who are scheduled to have unilateral TKA. Mean age: 68, 70, 68 ASA: not stated N=60	No outcomes	South Korea
General anaesthesia with nerve block and LIA versus general anaesthesia with nerve block				
Aso 2018[17]	All people had general anaesthesia induced with	Adults up to 85 years old undergoing primary TKA for	No outcomes	Japan

Study	Intervention and comparison	Population	Outcomes	Comments
	propofol, fentanyl, and rocuronium followed by continuous propofol and remifentanil. It was unclear how and when the femoral nerve block was administered. LIA undertaken after the bone cut. One group received LIA via ropivacaine, saline, and dexamethasone while the other received saline alone.	knee osteoarthritis Mean (SD) age: 72 (6) and 75 (6) ASA: not stated N=40		
Youm 2016[320]	All people had general anaesthesia and femoral nerve block using ropivacaine. One group had LIA before fixation of the implants using ropivacaine, morphine, epinephrine, methylprednisoline, ketorolac, cefoxitin, and saline.	People 80 years old or younger with osteoarthritis who are scheduled to have unilateral TKA. Mean age: 68, 70, 68 ASA: not stated N=60	No outcomes	South Korea

(a) <Insert Note here>

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical 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 Control	Risk difference with Regional versus general (95% CI)
Mortality	253 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias,	RR 0.9 (0.06 to 14.27)	8 per 1000	1 fewer per 1000 (from 8 fewer to 111 more)

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 versus general (95% CI)
		imprecision			
Mortality	Not reported				
Quality of life	Not reported				
Postoperative neurocognitive decline[3] Boston Naming. Scale from: 0 to 30.	253 (1 study) 1 weeks	⨁⨁⨀⨀ LOW[1] due to risk of bias		The mean postoperative neurocognitive decline in the control groups was 0	The mean postoperative neurocognitive decline in the intervention groups was 0.3 lower (0.93 lower to 0.33 higher)
Postoperative neurocognitive decline[3] Benton Visual Retention. Scale from: 0 to 10.	253 (1 study) 1 weeks	⨁⨁⨀⨀ LOW[1] due to risk of bias		The mean postoperative neurocognitive decline in the control groups was -0.8	The mean postoperative neurocognitive decline in the intervention groups was 0 higher (0.48 lower to 0.48 higher)
Postoperative neurocognitive decline[3] Wechsler Adult Intelligence Test. Scale from: 0 to 93.	253 (1 study) 1 weeks	⨁⨁⨀⨀ LOW[1] due to risk of bias		The mean postoperative neurocognitive decline in the control groups was -2.7	The mean postoperative neurocognitive decline in the intervention groups was 1 lower (2.49 lower to 0.49 higher)
Postoperative neurocognitive decline[3] Delirium	253 (1 study) 1 weeks	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.2 (0.59 to 2.44)	100 per 1000	20 more per 1000 (from 41 fewer to 144 more)
Thromboembolic complications DVT or PE	250 (2 studies) prior to discharge	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.93 (0.69 to 1.25)	412 per 1000	29 fewer per 1000 (from 128 fewer to 103 more)
Hospital readmission	Not reported				
Length of stay	253	⨁⨁⨀⨀		The mean length of stay in the	The mean length of stay in the

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 versus general (95% CI)
	(1 study)	LOW[1] due to risk of bias		control groups was 12.7 days	intervention groups was 0.6 lower (1.68 lower to 0.48 higher)
Mobilisation time until transfer unassisted	253 (1 study)	⨁⨁⊖⊖ LOW[1] due to risk of bias		The mean mobilisation in the control groups was 6.9 days	The mean mobilisation in the intervention groups was 0.3 lower (1.08 lower to 0.48 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] Neurocognitive decline outcomes could not be meta-analysed because the 3 continuous outcomes came from the same study and the 4th outcome was dichotomous.

1 **Table 4: Clinical evidence summary: Regional anaesthesia versus general 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 versus general with nerve block (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain Defence and Veterans Pain Rating Scale. Scale from: 0 to 10.	91 (1 study) 1 days	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean postoperative pain in the control groups was 3.3	The mean postoperative pain in the intervention groups was 0.8 higher (0.17 lower to 1.77 higher)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				

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 versus general with nerve block (95% CI)
Length of stay	91 (1 study)	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean length of stay in the control groups was 53 hours	The mean length of stay in the intervention groups was 6 hours higher (6.76 lower to 18.76 higher)
Mobilisation ambulating distance on postoperative day 1	85 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean mobilisation in the control groups was 235 metres	The mean mobilisation in the intervention groups was 89 lower (144.35 to 33.65 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.

Table 5: Clinical evidence summary: Regional anaesthesia with LIA versus general anaesthesia with LIA

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 with LIA versus general with LIA (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain	Not reported				
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications Pulmonary embolism	120 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1 (0.06 to 15.62)	17 per 1000	0 fewer per 1000 (from 16 fewer to 244 more)

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 with LIA versus general with LIA (95% CI)
Hospital readmission	Not reported				
Length of stay	120 (1 study)	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean length of stay in the control groups was 46 hours	The mean length of stay in the intervention groups was 6 higher (2.51 to 9.49 higher)
Nausea Morning and afternoon of day after surgery	240 (2 studies)	⨁⊖⊖⊖ VERY LOW[1,2,5] due to risk of bias, inconsistency, imprecision	RR -0.14 (-0.68 to 0.4)[4]	142 per 1000	140 fewer per 1000 (from 680 fewer to 400 more)[3]
Mobilisation within 24 hours after surgery	120 (1 study)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 0.98 (0.94 to 1.03)	1000 per 1000	20 fewer per 1000 (from 60 fewer to 30 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.
[3] Absolute effect calculated with risk difference
[4] Analysis with risk difference due to low events rate
[5] 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.

1 **Table 6: Clinical evidence summary: Regional anaesthesia with nerve block versus general 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 with nerve block versus general with nerve block (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain	88	⨁⨁⨁⊖		The mean postoperative	The mean postoperative pain in the

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 with nerve block versus general with nerve block (95% CI)
Defence and Veterans Pain Rating Scale. Scale from: 0 to 10.	(1 study) 1 days	MODERATE[1] due to imprecision		pain in the control groups was 3.3	intervention groups was 0.4 lower (1.24 lower to 0.44 higher)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Length of stay	88 (1 study)	⨁⨁⨁⨁ HIGH		The mean length of stay in the control groups was 53 hours	The mean length of stay in the intervention groups was 2 lower (13.84 lower to 9.84 higher)
Mobilisation ambulation distance on postoperative day 1	88 (1 study)	⨁⨁⨁⨀ MODERATE[2] due to risk of bias		The mean mobilisation in the control groups was 218 metres	The mean mobilisation in the intervention groups was 17 higher (39.45 lower to 73.45 higher)

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

1 **Table 7: Clinical evidence summary: General and regional anaesthesia versus general anaesthesia and 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 General and regional versus general and nerve block (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain no pain on movement	59 (1 study) during hospital recovery	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.49 (1.01 to 2.18)	533 per 1000	261 more per 1000 (from 5 more to 629 more)

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 and regional versus general and nerve block (95% CI)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Nausea/Vomiting	60 (1 study) prior to hospital discharge	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.5 (0.47 to 4.78)	133 per 1000	67 more per 1000 (from 71 fewer to 504 more)
Mobilisation within 24 hours after surgery Ability to perform a straight-leg raise	60 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.57 (0.19 to 1.75)	233 per 1000	100 fewer per 1000 (from 189 fewer to 175 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 8: Clinical 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 with LIA versus regional (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain VAS. Scale from: 0 to 10.	413 (6 studies[1]) 0-1 days	⨁⨁⊖⊖ LOW[2,3] due to risk of bias, imprecision		The mean postoperative pain in the control groups was 3	The mean postoperative pain in the intervention groups was 0.66 lower (1.13 to 0.2 lower)
Postoperative pain Person removed from study due to pain	56 (1 study) while still	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias,	Peto OR 0.13	103 per 1000	90 fewer per 1000 (from 102 fewer to 36 more)

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 with LIA versus regional (95% CI)
	admitted in hospital	imprecision	(0.01 to 1.35)		
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications Pulmonary embolism	250 (2 studies) unclear	⨁⊖⊖⊖ VERY LOW[2,3,4] due to risk of bias, inconsistency, imprecision	Peto OR 1 (0.14 to 7.01)	8 per 1000	0 fewer per 1000 (from 7 fewer to 48 more)
Hospital readmissions Treatment for stiffness or reoperation	400 (3 studies) within 6 weeks of surgery	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	RR 0.62 (0.24 to 1.61)	50 per 1000	19 fewer per 1000 (from 38 fewer to 31 more)
Postoperative use of analgesia Use of rescue medication	100 (1 study) 1 days	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	RR 0.78 (0.49 to 1.26)	460 per 1000	101 fewer per 1000 (from 235 fewer to 120 more)
Postoperative use of analgesia PCA use or narcotic consumption	419 (6 studies[1]) at varying in-hospital time points	⨁⊖⊖⊖ VERY LOW[2,3,4] due to risk of bias, inconsistency, 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 0.34 standard deviations lower (0.54 to 0.15 lower)
Length of stay	173 (3 studies)	⨁⊖⊖⊖ VERY LOW[2,3,4] due to risk of bias, inconsistency, imprecision		The mean length of stay in the control groups was 4.5 days	The mean length of stay in the intervention groups was 0.24 days higher (1.54 lower to 2.02 higher)
Nausea (or vomiting in 1 study)	275 (5 studies) varying in-hospital time	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	RR 0.90 (0.56 to 1.45)	169 per 1000	17 fewer per 1000 (from 75 fewer to 76 more)

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 with LIA versus regional (95% CI)
	points				

[1] 2 intervention groups from Han 2007 utilised in this analysis. Comparator group halved in size to prevent double counting.
[2] 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.
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis.

1 **Table 9: Clinical 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 with nerve block versus regional (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain Defence and Veterans Pain Rating Scale or VAS. Scale from: 0 to 10.	125 (2 studies) 2 hours after surgery or postoperative day 1	⊕⊕⊕⊕ HIGH		The mean postoperative pain in the control groups was 3.6	The mean postoperative pain in the intervention groups was 1.34 lower (2.01 to 0.68 lower)
Postoperative pain VAS >/= 6	80 (1 study) postoperative day 1	⊕⊕⊕⊖ MODERATE[1] due to risk of bias	RR 0.16 (0.04 to 0.66)	308 per 1000	258 fewer per 1000 (from 105 fewer to 295 fewer)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Postoperative use of analgesia	40	⊕⊕⊖⊖		The mean postoperative use	The mean postoperative use

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 with nerve block versus regional (95% CI)
Accumulated morphine consumption	(1 study) 1 days	LOW[1,2] due to risk of bias, imprecision		of analgesia in the control groups was 28 mg	of analgesia in the intervention groups was 10.08 lower (17.88 to 2.28 lower)
Length of stay	85 (1 study)	⊕⊕⊕⊖ MODERATE[2] due to imprecision		The mean length of stay in the control groups was 59 hours	The mean length of stay in the intervention groups was 8 lower (16.5 lower to 0.5 higher)
Nausea	40 (1 study) while in hospital	⊕⊕⊖⊖ LOW1[,5] due to risk of bias, imprecision	RD 0 (-0.09 to 0.09)[4]	See comment	0 fewer per 1000 (from 90 fewer to 90 more)[3]
Mobilisation: Ambulation distance on postoperative day 1	85 (1 study) 1 days	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean mobilisation: in the control groups was 146 metres	The mean mobilisation: in the intervention groups was 89 higher (33.65 to 144.35 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] Analysed using risk difference due to zero events in both groups
[5] Downgraded one increment for imprecision as it is a small study with no events.

1 **Table 10: Clinical evidence summary: Regional anaesthesia with LIA versus regional anaesthesia with nerve block**

Outcomes	No of Participants	Quality of the	Relati	Anticipated absolute effects

	(studies) Follow up	evidence (GRADE)	ve effect (95% CI)	Risk with Control	Risk difference with Regional with LIA versus regional with nerve block (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain VAS or NRS. Scale from: 0 to 10.	319 (4 studies) all at some point before the end of postoperative day 1	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean postoperative pain in the control groups was 4	The mean postoperative pain in the intervention groups was 0.95 lower (1.5 to 0.39 lower)
Postoperative pain time to onset	200 (1 study)	⊕⊕⊕⊖ MODERATE[1] due to risk of bias		The mean postoperative pain in the control groups was 15.3 hours	The mean postoperative pain in the intervention groups was 6.9 lower (9.34 to 4.46 lower)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications DVT	70 (1 study) unclear	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.14 (0.0 to 6.82)	29 per 1000	25 fewer per 1000 (from 29 fewer to 166 more)
Hospital readmissions For irrigation, debridement and polythene exchange	40 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 7.39 (0.15 to 372.38)	0 per 1000	50 more per 1000 (from 80 fewer to 180 more)[3]
Postoperative use of analgesia Number of suppositories used	200 (1 study) 48 hours after surgery	⊕⊕⊕⊖ MODERATE[1] due to risk of bias		The mean postoperative use of analgesia in the control groups was 2.8 suppositories	The mean postoperative use of analgesia in the intervention groups was 0.1 higher (0.27 lower to 0.47 higher)

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 with LIA versus regional with nerve block (95% CI)
Postoperative use of analgesia Usage in mg	389 (5 studies) varying time points no later than postoperative day 3	⨁⊖⊖⊖ VERY LOW[1,2,4] due to risk of bias, inconsistency, imprecision		The mean postoperative use of analgesia ranged across control groups from 7-176.5 mg	The mean postoperative use of analgesia in the intervention groups was 0.29 standard deviations lower (0.61 lower to 0.03 higher)
Length of stay	214 (4 studies)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias		The mean length of stay in the control groups was 4.5 days	The mean length of stay in the intervention groups was 0.29 lower (0.61 lower to 0.03 higher)
Nausea (and vomiting in one paper)	240 (2 studies) unclear	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.32 (0.59 to 2.94)	75 per 1000	24 more per 1000 (from 31 fewer to 146 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.
[3] Absolute effect calculated using the risk difference. RD: 0.05 [-0.08, 0.18]
[4] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.

1 **Table 11: Clinical evidence summary: Regional anaesthesia with nerve block and LIA versus regional anaesthesia with LIA**

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 with nerve block and LIA versus regional with LIA (95% CI)
Mortality	Not reported				
Quality of life	Not reported				

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 with nerve block and LIA versus regional with LIA (95% CI)
Postoperative pain Requiring rescue IV PCA	130 (1 study) in-hospital period	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.81 (0.52 to 1.26)	419 per 1000	80 fewer per 1000 (from 201 fewer to 109 more)
Postoperative pain VAS or NRS. Scale from: 0 to 10.	287 (3 studies) varying within 1 day of surgery	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision		The mean postoperative pain in the control groups was 4	The mean postoperative pain in the intervention groups was 1.8 lower (2.34 to 1.27 lower)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Postoperative use of analgesia Opioid consumption	417 (4 studies) varying within 3 days of surgery	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision		The mean postoperative use of analgesia ranged across control groups from 5-100 mg	The mean postoperative use of analgesia in the intervention groups was 0.24 standard deviations lower (0.43 to 0.05 lower)
Length of stay	102 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to risk of bias		The mean length of stay in the control groups was 2.5 days	The mean length of stay in the intervention groups was 0 higher (0.66 lower to 0.66 higher)
Nausea or vomiting	130 (1 study) while in hospital	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 0.87 (0.66 to 1.14)	661 per 1000	86 fewer per 1000 (from 225 fewer to 93 more)
Mobilisation	85	⨁⨁⨁⨀		The mean mobilisation in the	The mean mobilisation in the

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 with nerve block and LIA versus regional with LIA (95% CI)
Distance walked on postoperative day 1	(1 study)	MODERATE[2] due to imprecision		control groups was 81 metres	intervention groups was 6.6 higher (16.44 lower to 29.64 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] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.

1 **Table 12: Clinical evidence summary: Regional anaesthesia with nerve block and 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 with nerve block and LIA versus regional with nerve block (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain VAS or NRS. Scale from: 0 to 10.	240 (3 studies) varies within 1 day surgery	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision		The mean postoperative pain in the control groups was 5	The mean postoperative pain in the intervention groups was 1.72 lower (2.26 to 1.17 lower)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Postoperative use of analgesia	240 (3 studies) varies within 3	⨁⨁⊖⊖ LOW[1,3] due to risk of bias,		The mean postoperative use of analgesia ranged across control groups from	The mean postoperative use of analgesia in the intervention groups was

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 with nerve block and LIA versus regional with nerve block (95% CI)
Opioid consumption	days of surgery	imprecision		7-131 mg	0.66 standard deviations lower (0.92 to 0.4 lower)
Length of stay	171 (2 studies)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias		The mean length of stay in the control groups was 3.5 days	The mean length of stay in the intervention groups was 0.18 lower (0.53 lower to 0.18 higher)
Nausea	40 (1 study) within 24 hours of surgery	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	RR 0.5 (0.05 to 5.08)	100 per 1000	50 fewer per 1000 (from 95 fewer to 408 more)
Mobilisation within 24 hours after surgery	32 (1 study)	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 9.94 (1.52 to 65.02)	0 per 1000	310 more per 1000 (from 80 more to 550 more)[4]

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Absolute effect calculated using the risk difference. RD: 0.31 [0.08, 0.55]]

1 **Table 13: Clinical 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 with LIA versus general (95% CI)
Mortality	Not reported				

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 with LIA versus general (95% CI)
Quality of life	Not reported				
Postoperative pain	Not reported				
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications Proximal DVT	48 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	RR 7.39 (0.15 to 372.38)	0 per 1000	40 more per 1000 (from 70 fewer to 150 more)[1]
Hospital readmission	Not reported				
Length of stay	48 (1 study)	⨁⨁⊖⊖ LOW[2,3] due to risk of bias, imprecision		The mean length of stay in the control groups was 142 hours	The mean length of stay in the intervention groups was 16 lower (47.12 lower to 15.12 higher)
Nausea	48 (1 study) unclear	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	RR 0.82 (0.42 to 1.61)	458 per 1000	82 fewer per 1000 (from 266 fewer to 280 more)

[1] Absolute effect calculated using the risk difference. RD: 0.04 (-0.07, 0.15)
[2] 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
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 14: Clinical 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 with nerve block versus general (95% CI)
Mortality	Not reported				

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 with nerve block versus general (95% CI)
Quality of life	Not reported				
Postoperative pain VAS at rest on postoperative day 0. Scale from: 0 to 100.	91 (2 studies[1])	⨁⊖⊖⊖ VERY LOW[2,3,4] due to risk of bias, inconsistency, imprecision		The mean postoperative pain in the control groups was 48	The mean postoperative pain in the intervention groups was 10.34 lower (32.03 lower to 11.35 higher)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Postoperative use of analgesia Morphine consumption via PCA in mg on postoperative day 0	91 (2 studies[1])	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, inconsistency		The mean postoperative use of analgesia in the control groups was 22 mg	The mean postoperative use of analgesia in the intervention groups was 13.54 lower (25.74 to 1.34 lower)

[1] Both results from the same study but utilising different treatment groups
[2] 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.
[3] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

1 **Table 15: Clinical evidence summary: General anaesthesia with LIA versus general 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 General with LIA versus general with nerve block (95% CI)
Mortality	Not reported				
Quality of life	Not reported				

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 with LIA versus general with nerve block (95% CI)
Postoperative pain	Not reported				
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications	Not reported				
Hospital readmission	Not reported				
Postoperative use of analgesia Opioid consumption	75 (1 study) 48 hours after surgery	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean postoperative use of analgesia in the control groups was 51 mg	The mean postoperative use of analgesia in the intervention groups was 2.99 lower (8.1 lower to 2.12 higher)
Length of stay	115 (2 studies)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean length of stay in the control groups was 5.15 days	The mean length of stay in the intervention groups was 0.24 lower (0.44 to 0.05 lower)
Mobilisation 24 or 31 hours after surgery Varying: walking 10m or mobilised to stand	115 (2 studies) postoperative day 1	⨁⨁⊖⊖ LOW[1] due to risk of bias	RR 1.01 (0.93 to 1.08)	981 per 1000	10 more per 1000 (from 69 fewer to 79 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 16: Clinical evidence summary: General anaesthesia with nerve block and LIA versus general anaesthesia with LIA

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 with nerve block and LIA versus general with LIA (95% CI)

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 with nerve block and LIA versus general with LIA (95% CI)
Mortality	Not reported				
Quality of life	Not reported				
Postoperative pain Unclear scale. Scale from: 0 to 4.	55 (1 study) 24 hours after surgery	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean postoperative pain in the control groups was 2.5	The mean postoperative pain in the intervention groups was 0.1 lower (0.58 lower to 0.38 higher)
Postoperative neurocognitive decline	Not reported				
Thromboembolic complications Thromboembolic events	55 (1 study) while in hospital	⨁⊖⊖⊖ VERY LOW[1,5] due to risk of bias, imprecision	RD 0 (-0.07 to 0.07)[4]	0 per 1000	0 fewer per 1000 (from 70 fewer to 70 more)[3]
Hospital readmission	Not reported				
Postoperative use of analgesia Fentanyl use via PCA	55 (1 study) within 24 hours of surgery	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean postoperative use of analgesia in the control groups was 1.5 mg	The mean postoperative use of analgesia in the intervention groups was 0.53 lower (0.84 to 0.22 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.
[3] Absolute effect calculated using the risk difference
[4] Analysis by 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.

1

2 See appendix F for full GRADE tables.

1

1.5 Economic evidence

1.5.1 Included studies

One health economic study was identified with the relevant comparison and has been included in this review. [170] The study is summarised in the health economic evidence profile below (Table 17) 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.

1.5.3 Summary of studies included in the economic evidence review

Table 17: 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[170] [UK]	Partially applicable[(a)]	Potentially serious 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 TKR with a 12 month time horizon.	LAI in addition to a standard anaesthetic regimen saved £77 per person.	LAI in addition to a standard anaesthetic regimen gave 0.009 more QALYS per person.	LAI in addition to a standard anaesthetic regimen dominates (less costly and more effective) standard anaesthetic alone.	A series of probabilistic sensitivity analyses (excluding PSS costs, macro-costing and varying local inpatient costs) were conducted. The dominance of the intervention was robust to all scenarios. In the base case LAI was cost effective at a threshold of £20,000 per QALY gained in 60% of simulations.

Abbreviations: LAI; local anaesthetic wound infiltration; PSS; public and social services; QALY= quality-adjusted life years; RCT= randomised controlled trial; TKR: total knee 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 142/316 (45%) 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 a femoral nerve block in addition to spinal or general anaesthesia

(d) This study was excluded from the clinical review as it was not possible to determine if participants had received spinal or general anaesthesia. It has been included as economic evidence as it may still provide useful cost information

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

Table 18 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 18: 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)[49]; CG124[196]

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

(b) It was assumed that the cost of theatre time from CG124[196] did not include personnel costs

(c) NHS Hospital is Peterborough and Stamford Hospitals NHS Foundation Trust which provided information for CG124[196]

1.6 Evidence statements

1.6.1 Clinical evidence statements

Thirty-eight RCTs covering 15 comparisons were included in the evidence review and relevant outcomes were extracted for 14 of the comparisons.

Regional anaesthesia versus general anaesthesia was compared in 2 RCTs (n=234) and all outcomes were graded at low or very low quality. No difference was found for mortality, 2 postoperative neurocognitive decline outcomes, thromboembolic complications, length of stay, and mobilisation. A benefit for general anaesthesia was seen in 2 other neurocognitive decline outcomes. No outcomes favoured regional anaesthesia.

Regional anaesthesia versus general anaesthesia with nerve block was compared in 1 RCT (n=99) and all outcomes were graded at low or very low quality. No difference was found for

postoperative pain and length of stay. There was a benefit for general anaesthesia with nerve block in terms of mobilisation. No outcomes favoured regional anaesthesia.

Regional anaesthesia with LIA versus general anaesthesia with LIA was compared in 1 RCT (n=120) and 1 outcome graded moderate quality, 1 low quality and 2 at very low quality. No difference was found for thromboembolic complications, nausea, and mobilisation. There was a benefit for general anaesthesia with LIA in length of stay. No outcomes favoured regional anaesthesia with LIA.

Regional anaesthesia with nerve block versus general anaesthesia with nerve block was compared in 1 RCT (n=94) and 1 outcome graded high quality and 2 moderate quality. No outcomes indicated a benefit of either treatment and these were postoperative pain, length of stay, and mobilisation.

General with regional anaesthesia versus general anaesthesia and nerve block was compared in 2 RCTs (n=126) and all outcomes graded very low quality. There was a benefit for general with regional anaesthesia in postoperative pain. Nausea and mobilisation outcomes indicated a benefit of general anaesthesia and nerve block.

Regional anaesthesia with LIA versus regional anaesthesia was compared in 8 RCTs (n=686) and all but 1 outcome was graded very low quality. There was a benefit for regional anaesthesia with LIA in 1 postoperative pain outcome (1 RCT), hospital readmission, and 1 postoperative use of analgesia outcome (1 RCT). No difference was seen for a second postoperative pain outcome (6 RCTs), thromboembolic complications, a second postoperative use of analgesia outcome (6 RCTs), length of stay, and nausea. No outcomes favoured regional anaesthesia alone.

Regional anaesthesia with nerve block versus regional anaesthesia were compared in 4 RCTs (n=292) and quality ranged from high to low. A benefit was seen for regional anaesthesia with nerve block in terms of 2 postoperative pain outcomes, postoperative use of analgesia, and mobilisation. There was no difference between interventions in length of stay and nausea. No outcomes favoured regional anaesthesia alone.

Regional anaesthesia with LIA versus regional anaesthesia with nerve block were compared in 8 RCTs (n=736) and quality ranged from moderate to very low. A benefit for regional anaesthesia with nerve block was found for 1 postoperative pain outcome (1 RCT), hospital readmissions, and nausea. Regional anaesthesia with LIA was more effective for thromboembolic complications. There was no difference for a second postoperative pain outcome (4 RCTs), 2 postoperative use of analgesia outcomes, and length of stay.

Regional anaesthesia with nerve block and LIA versus regional anaesthesia with LIA were compared in 4 RCTs (n=427) and quality ranged from moderate to very low. Regional anaesthesia with nerve block and LIA were more effective in a postoperative pain outcome (3 RCTs). All other outcomes indicated no clinical difference between interventions, these was a second postoperative pain outcome (1 RCT), postoperative use of analgesia, length of stay, nausea, and mobilisation.

Regional anaesthesia with nerve block and LIA versus regional anaesthesia with nerve block alone were compared in 5 RCTs (n=343) and quality ranged from moderate to very low. 4 of 5 outcomes indicated a benefit of using regional anaesthesia with nerve block and LIA, these were postoperative pain, postoperative use of analgesia, nausea, and mobilisation. There was no clinical difference between interventions in terms of length of stay.

General anaesthesia with LIA versus general anaesthesia were compared in 1 RCT (n=48) and quality was graded low or very low for all outcomes. There was a clinically important benefit for general anaesthesia in thromboembolic complications. Length of stay and nausea did not find any difference between interventions. No outcomes favoured general anaesthesia with LIA.

General anaesthesia with nerve block versus general anaesthesia were compared in 1 RCT (n=107)and both outcomes were graded very low quality. General anaesthesia with nerve block was found to be more effective for postoperative use of analgesia however no difference was found for postoperative pain. No outcomes favoured general anaesthesia alone.

General anaesthesia with LIA versus general anaesthesia with nerve block were compared in 3 RCTs (n=175) and outcomes were graded low or very low quality. General anaesthesia with LIA was found to be more effective in terms of length of stay. The other 2 outcomes found no difference between interventions, these were postoperative use of analgesia and mobilisation.

General anaesthesia with nerve block and LIA versus general anaesthesia with LIA were compared in 3 RCTs (n=161) though only 1 RCT (n=55) provided outcomes and these were all graded very low quality. A benefit for general anaesthesia with nerve block and LIA was found for postoperative use of analgesia. No difference between interventions was found for postoperative pain and thromboembolic complications. No outcomes favoured general anaesthesia with LIA.

General anaesthesia with nerve block and LIA versus general anaesthesia with nerve block were compared in 2 RCTs (n=100). However no relevant outcomes could be extracted.

1.6.2 Health economic evidence statements

One cost utility analysis found that using local anaesthetic wound infiltration in addition to a femoral nerve block and regional or general anaesthesia was dominant (less costly and more effective) compared to femoral nerve block, regional or general anaesthesia alone in people undergoing total knee 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 time horizon 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 agreed by the guideline committee were mortality, quality of life, postoperative pain, postoperative neurocognitive decline, thromboembolic complications, and hospital readmission. The time point for mortality, the most critical outcome, was specified as 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 equalise these factors between treatment groups. Postoperative pain is of critical importance as it represents a central aspect person's initial

experience of the joint replacement surgery. In addition the committee agreed that there is an argument that acute pain is a predictor of chronic pain and therefore reducing postoperative pain 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 a very important 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 though the great majority were assessed as low or very low quality.

The outcome quality was often downgraded due to 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 downgrading quality due to risk of bias was due to the difficulty of blinding in surgical treatment which meant subjective outcomes were occasionally assessed by people who knew the anaesthetic treatment utilised. Outside of those some studies had missing data and were downgraded for that.

More than half of the outcomes were downgraded in quality due to imprecision and more than ten percent was downgraded for inconsistency. This was not explained by subgroup analysis and a random effects model was utilised.

1.7.1.3 Benefits and harms

36 randomised controlled trials were included in the evidence review. These trials encompassed 15 comparisons though relevant evidence was only found for 14 of the comparisons. The studies investigating the 15th comparison did not provide relevant outcomes for analysis. 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. A number of studies were excluded due to nerve block being utilised in the postoperative period and the protocol for this evidence review states that only LIA can be started in the postoperative period.

The committee commented that most of the studies included in the review concentrated on comparisons involving regional anaesthesia in both treatment groups. There were many fewer studies comparing general anaesthesia in both groups or regional anaesthesia to general anaesthesia. It was suggested that having relatively few studies for those comparisons may have led to the less definitive results.

The committee spoke about the results of comparisons involving nerve block in the treatment. Many of the studies utilised femoral nerve blocks (FNB) but modern care has shifted towards Adductor Canal Blocks (ACB). FMBs have a motor component that is thought

to lead to make early mobilisation more difficult and consequently lead to longer length of stays. ACB only block sensory nerves and this leads to faster recovery. The committee agreed that the use of FNBs could have negatively biased the results in length of stay and mobilisation outcomes unfairly given the modern prominence of ACBs and the results should be interpreted with that in mind.

The committee agreed that the results of the review did not distinguish either regional anaesthesia or general anaesthesia from the other. There was little evidence for using a combination of the two and it is rarely used this way in NHS practice. Therefore a recommendation was made to offer either regional anaesthesia or general anaesthesia for primary elective total knee replacements. However the results within the regional anaesthesia with or without augmentation versus regional anaesthesia with or without augmentation comparisons indicated benefits with the addition of a nerve block or LIA. Additionally it indicated that adding both nerve block and LIA on top of regional anaesthesia was more effective than offering regional with either one alone. The results for general anaesthesia with or without augmentation versus general anaesthesia with or without augmentation were less clear cut. The committee commented that where the results favoured one treatment, it was in all but one case the treatment with the combination treatment with LIA and/or nerve block. However the majority of the results indicated no clinical difference between the treatments. The committee agreed that it was important to leave room in the recommendations for the anaesthetist to use their expertise and experience to modify the anaesthesia and analgesia where it makes clinical sense.

1.7.2 Cost effectiveness and resource use

The evidence presented showed that the addition of LIA to a nerve block and regional or general anaesthesia was cost effective. The cost savings in the economic evidence were driven by reduced costs of inpatient admissions after initial discharge in the LAI group. There was consensus that using LIA is unlikely to represent additional costs in terms of time or personnel as it is often administered in redundant theatre time. However, the committee thought the evidence was limited given that there was no sub-group analysis for those who received general or regional anaesthesia. The cost savings or health gains could have been driven by either of these groups. There was no economic evidence presented for the addition of a nerve block to an anaesthetic regimen. Current practice is varied; some surgeons will only offer LAI in addition to general or regional whereas others will only offer nerve blocks in addition to general or regional.

For general anaesthesia using a volatile agent is cheaper than using total intravenous anaesthesia (TIVA), although the quality of recovery may be reduced. There are myriad factors, aside from the agents themselves, which can affect the overall cost of anaesthesia. However, it was agreed that regional anaesthesia is likely to be less costly than general anaesthesia. Despite this, general anaesthesia should still be available for those who are contraindicated for regional anaesthesia.

The intervention in the included study factored in a femoral nerve block. However, standard practice of nerve blocks, if used, has now moved away from femoral nerve blocks to adductor canal blocks. An adductor canal 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.

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

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

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

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

The committee acknowledged that the time required for administration and the inclusion of the cost of theatre time was dependent on the experience of the anaesthetist and if two anaesthetists are available, respectively. All combinations of personnel numbers and time taken for administration can be found on the NHS at present. The length of time that nerve blocks have an effect could be argued to be anything between a matter of hours to a lifetime. The analgesic effect of a nerve block is variable but may be 8 hours on average for knee replacements. However, a 24 hour time horizon may be the most appropriate when considering acute post-operative outcomes (for example, pain, post-operative nausea and vomiting). A longer time horizon of 10 days to 30 days may be most appropriate to account for the possible effect of anaesthetic choice on adverse clinical outcomes (for example post-operative morbidity and mortality). Lastly, an even longer time horizon would be needed to account for long term outcomes (such as chronic pain, opioid dependence and range of motion).

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 effective and likely to be 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 on top of LIA 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 in addition to LIA and regional or general anaesthesia. There were roughly 84,000 total knee replacements in 2017, all of which require some form of anaesthetic. All orthopaedic units currently offer a choice of general or regional anaesthesia. Most augment this with either LIA or a nerve block or both. 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.

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Appendices

Appendix A: Review protocols

Table 19: Review protocol: anaesthesia in knee joint replacement surgery

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

ID	Field	Content
		The full search strategies will be published in the final review.
5.	Condition or domain being studied	Primary elective knee joint replacement surgery
6.	Population	Inclusion: Adults having primary elective knee 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 (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)
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.

ID	Field	Content
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	Mortality: upto 90 days (dichotomous) Quality of life up to 30 days (continuous) Postoperative pain up to 30 days (continuous) Postoperative neurocognitive decline up to 30 days (dichotomous) Thromboembolic complications up to 90 days (VTE; dichotomous) 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

ID	Field	Content	
		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. 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

ID	Field	Content		
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	01/02/19		
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]		

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

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

1

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Table 20: 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).[195] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example,

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

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[195]

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 21: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

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

1 **Embase (Ovid) search terms**

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

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

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

1 **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

2 **Epistemonikos search terms**

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

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

1

B.2 Health Economics literature search strategy

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

8 **Table 22: 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

9 **Medline (Ovid) search terms**

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

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

1 **Embase (Ovid) search terms**

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

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

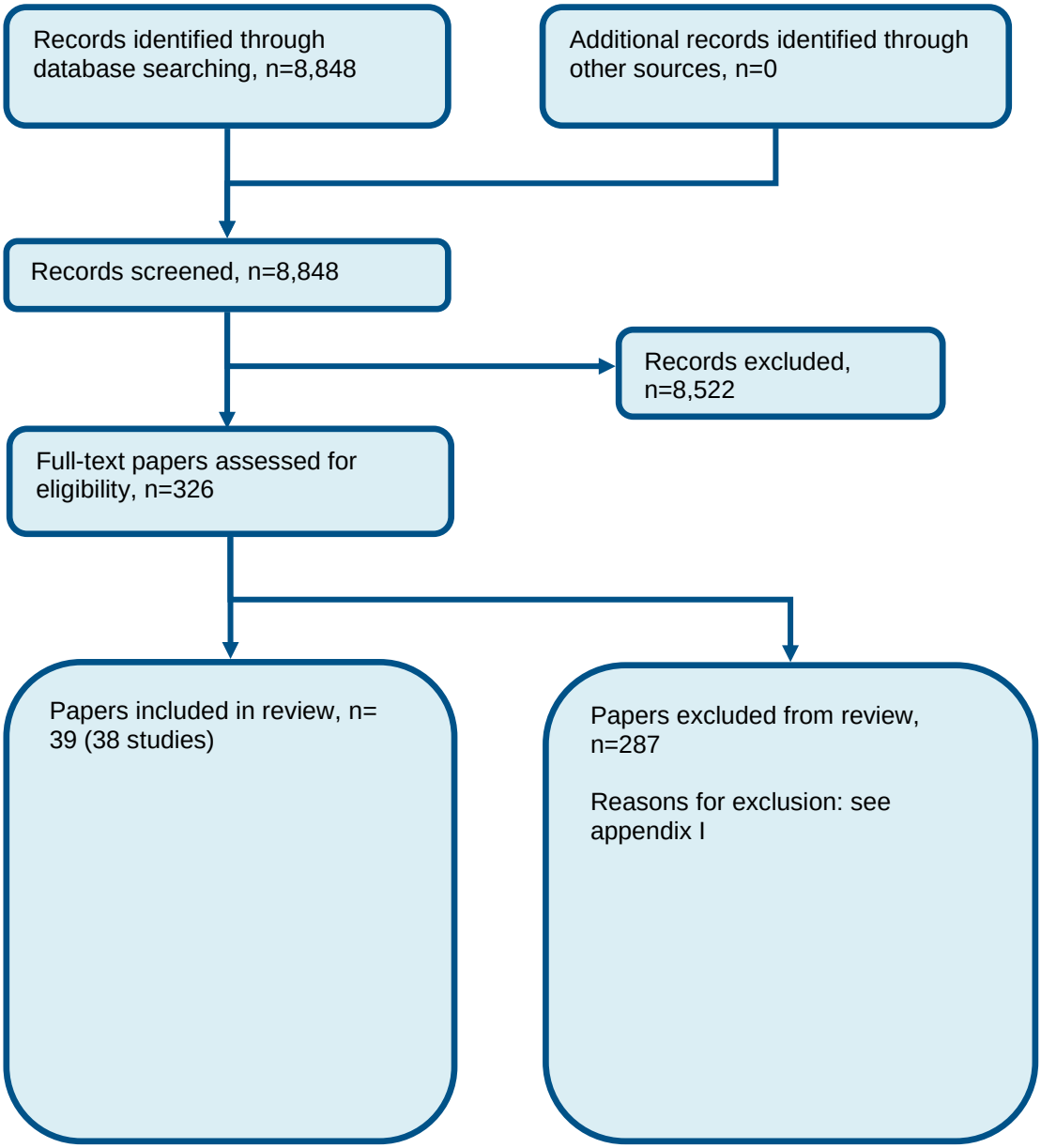
1 **NHS EED and HTA (CRD) search terms**

#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

2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of anaesthesia for knee replacement surgery



Appendix D: Clinical evidence tables

Study	Ashraf 2013[16]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery 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 to undergo primary TKR
Exclusion criteria	Lacked capacity to consent to the study, unwilling to consent to the study, known allergy to study medication, unable to have spinal anaesthesia.
Recruitment/selection of patients	Recruited from 3 consultants patients.
Age, gender and ethnicity	Age - Other: Not detailed. Gender (M:F): Not detailed. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia using bupivacaine. Single shot ultrasound guided femoral nerve block using ropivacaine. . Duration Surgery and in hospital period. Concurrent medication/care: People sedated with propofol. Postoperative analgesia as required via PCA, oxycodone, paracetamol and NSAIDs. . Indirectness: No indirectness (n=20) Intervention 2: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacaine. LIA into all layers of the knee joint using ropivacaine, adrenaline and ketorolac. . Duration Surgery and in hospital period. Concurrent medication/care: People sedated with propofol. Postoperative analgesia as required via PCA, oxycodone, paracetamol and NSAIDs. . Indirectness: No indirectness

Funding	Funding not stated (It was stated 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 pain at within 30 days
- Actual outcome: Pain at 2 hours after surgery; Group 1: mean 1.6 (SD 2.4); n=19, Group 2: mean 3.6 (SD 3.2); n=21; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Very 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: 1, Reason: Did not receive allocated intervention; Group 2 Number missing: 1, Reason: Did not receive allocated intervention

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Postoperative equivalent IV morphine consumed at Postoperative day 1; Group 1: mean 115 mg (SD 50.3); n=19, Group 2: mean 176.5 mg (SD 103.2); n=21
Risk of bias: All domain - Very high, Selection - Very 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: 1, Reason: Did not receive allocated intervention; Group 2 Number missing: 1, Reason: Did not receive allocated intervention

Protocol outcome 3: Length of stay at .
- Actual outcome: Length of stay at .; Group 1: mean 5.4 days (SD 1.2); n=19, Group 2: mean 5.7 days (SD 1.3); n=21
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, Reason: Did not receive allocated intervention; Group 2 Number missing: 1, Reason: Did not receive allocated intervention

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; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Aso 2018[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Japan; Setting: Single institution
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 months 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 TKA for knee osteoarthritis
Exclusion criteria	Bilateral TKA, people over 85 years of age, body weight under 40kg, inflammatory arthritis, kidney dysfunction, diabetes, psychiatric conditions.
Age, gender and ethnicity	Age - Mean (SD): 72 (6) and 75 (6). Gender (M:F): 7/33. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: General - General anaesthesia with nerve block and local infiltration analgesia (during or after procedure). General anaesthesia induced with propofol, fentanyl, and rocuronium followed by continuous propofol and remifentanil. After the bone cut, ropivacaine, saline, and dexamethasone injected into peri-articular tissues. These sites included the synovium and joint capsule. It was unclear how and when the nerve block was administered. . Duration Surgery and 14 days postoperatively . Concurrent medication/care: At the end of surgery flurbiprofen and fentanyl administered intravenously. PCA used for 48 hours after surgery. Oral loxoprofen until postoperative day 5 and oral acetaminophen until postoperative day 14 were given. . Indirectness: No indirectness (n=20) Intervention 2: General - General anaesthesia with nerve block. General anaesthesia induced with propofol, fentanyl, and rocuronium followed by continuous propofol and remifentanil. It was unclear how and when the nerve block was administered. . Duration Surgery and 14 days postoperatively . Concurrent medication/care: At the end of surgery flurbiprofen and fentanyl administered intravenously. PCA used for 48 hours after surgery. Oral loxoprofen until postoperative day 5 and oral acetaminophen until postoperative day 14 were given. . Indirectness: No indirectness
Funding	No 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 .

Study	Biswas 2018[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=201)
Countries and setting	Conducted in Canada; Setting: Toronto Western Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People capable of ambulating independently, 18-80 years old, BMI 18-40, ASA I-III undergoing elective unilateral TKA.
Exclusion criteria	Revision, bilateral TKA, contraindications to regional anaesthesia, existing neuropathic pain or neurologic disorder of the surgical limb, preoperative opioid therapy.
Recruitment/selection of patients	January 2014 to September 2016.
Age, gender and ethnicity	Age - Mean (SD): 64 (8), 64 (8), 65 (9). Gender (M:F): 81/113. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=69) Intervention 1: Regional - Regional anaesthesia with nerve block and local infiltration analgesia (during or after surgery). Adductor canal block (ACB). Spinal anaesthesia using bupivacaine. LIA through ropivacaine, ketorolac and epinephrine. Solution administered intraoperatively: half before insertion of implants and the other half before skin closure. . Duration Surgery and follow up for 5 days. Concurrent medication/care: Midazolam and fentanyl used for sedation. Postoperative multimodal oral analgesics given: acetaminophen, celecoxib, NSAIDs, hydromorphone, oxycodone. . Indirectness: No indirectness (n=65) Intervention 2: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Sham adductor canal block (ACB). Spinal anaesthesia using bupivacaine. LIA through ropivacaine, ketorolac and epinephrine. Solution administered intraoperatively: half before insertion of implants and the other half before skin closure. . Duration Surgery and follow up for 5 days. Concurrent medication/care: Midazolam and fentanyl used for sedation. Postoperative multimodal oral analgesics given: acetaminophen, celecoxib, NSAIDs, hydromorphone, oxycodone. . Indirectness: No indirectness
Funding	Funding not stated

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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Uncontrolled pain: requiring rescue IV PCA at Within hospital period; Group 1: 23/68, Group 2: 26/62
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: Protocol violation; Group 2 Number missing: 3, Reason: Protocol violation

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Opioid requirements at 12 hours after surgery; Group 1: mean 12 mg (SD 14); n=68, Group 2: mean 16 mg (SD 19); n=62
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: Protocol violation; Group 2 Number missing: 3, Reason: Protocol violation

Protocol outcome 3: Nausea at within 30 days
- Actual outcome: Nausea/vomiting at Within hospital period; Group 1: 39/68, Group 2: 41/62
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: Protocol violation; Group 2 Number missing: 3, Reason: Protocol violation

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; Length of stay at .; Mobilisation within 24 hours after surgery at .

Study	Chan 2014[36]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Taiwan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 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 40-80 years old, ASA I-III, scheduled for unilateral, primary TKA.
Exclusion criteria	Known hypersensitivities to any of the test substances used in this study, a history of substance abuse, contraindications to spinal anesthesia, having femoral neuropathy or a poor ability to communicate. Premedication was omitted.
Age, gender and ethnicity	Age - Mean (SD): 68 (9) and 71 (9). Gender (M:F): 9/31. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Regional - Regional anaesthesia with nerve block. Spinal anesthesia with hyperbaric bupivacaine at the L2-5 interspace followed by femoral Nerve Block with bupivacaine and epinephrine.. Duration In hospital period. Concurrent medication/care: Intraoperative sedation with incremental midazolam of was left to the discretion of the anesthesiologist in charge. A PCA pump was started to convey morphine hydrochloride when the patient arrived in the post anesthesia care unit (PACU).. Indirectness: No indirectness (n=20) Intervention 2: Regional - Regional anaesthesia. Spinal anesthesia with hyperbaric bupivacaine at the L2-5 interspace followed by sham femoral Nerve Block with saline.. Duration In hospital period. Concurrent medication/care: Intraoperative sedation with incremental midazolam of was left to the discretion of the anesthesiologist in charge. A PCA pump was started to convey morphine hydrochloride when the patient arrived in the post anesthesia care unit (PACU).. Indirectness: No indirectness
Funding	Academic or government funding (VGHKS98-065, VGHKS97-084 from Kaohsiung Veterans General Hospital)

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 1.7 (SD 1.5); n=20, Group 2: mean 3.2 (SD 1.6); n=20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Accumulated morphine consumption at 24 hours after surgery; Group 1: mean 18.24 mg (SD 12.68); n=20, Group 2: mean 28.32 mg (SD 12.48); n=20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Nausea at within 30 days
- Actual outcome: Nausea at Inpatient period; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality at within 90 days; Quality of life at within 30 days; Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days; Length of stay at .; Mobilisation within 24 hours after surgery at .

Study	Choi 2016[43]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Canada; Setting: 2 tertiary care academic health centers.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 4.5 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults 85 years old or younger, ASA I-III., scheduled to undergo primary tricompartmental TKA
Exclusion criteria	Allergy, intolerance, contraindication to any study medications, inability to walk independently before TKA, inability to comprehend French or English, use of antipsychotics, BMI >40, opioid tolerance.
Recruitment/selection of patients	July 2012 to October 2012.
Age, gender and ethnicity	Age - Mean (SD): 64 (7), 65 (9), 66 (8). Gender (M:F): 58/63 (as reported). Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia using bupivacauine and fentanyl. Single injection femoral nerve block using ropivacaine. Sham LIA using saline. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, celecoxib, gabapentin. Postoperative medication: PCA using hydromorphone. Acetaminophen, celecoxib, and gabapentin administered. . Indirectness: No indirectness (n=41) Intervention 2: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacauine and fentanyl. Sham femoral nerve block. Intraoperative LIA using ropivacaine, epinephrine, and ketorolac. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, celecoxib, gabapentin. Postoperative medication: PCA using hydromorphone. Acetaminophen, celecoxib, and gabapentin administered. . Indirectness: No indirectness
Funding	Academic or government funding (Supported by Canadian Anesthesia Research Foundation (CARF) in Toronto, Physicians' Services Incorporated Foundation (PSI) in Toronto, Department of Anesthesia at Sunnybrook Health Sciences Centre.)

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 pain at within 30 days - Actual outcome: Pain at rest at 9am on postoperative day 1; Group 1: mean 2.5 (SD 2.3); n=41, Group 2: mean 3.9 (SD 2.2); n=39; Numerical Rating Scale 0-10 Top=High is poor outcome 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: Postoperative use of analgesia at as reported - Actual outcome: Equivalent morphine consumption at 48 hours after surgery; Group 1: mean 77.2 mg (SD 40.8); n=41, Group 2: mean 93.7 mg (SD 45.2); n=39 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 neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Davies 2004[51]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	--: Surgery and 48 hour follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults undergoing unilateral primary total knee replacement
Exclusion criteria	ASA classification >3 or had a contraindication to the use of non-steroidal anti-inflammatory drugs, local anaesthetic agent, neuraxial blockade or tourniquet usage; painful polyarthralgia.
Age, gender and ethnicity	Age - Mean (SD): 73 (9) and 72 (10). Gender (M:F): 32/28. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: General and regional - General and regional anaesthesia. Neural blocks were inserted before induction of anaesthesia. Epidural catheter utilised with an infusion of bupivacaine commenced after surgical incision.General anaesthesia was induced with propofol and fentanyl. Anaesthesia was maintained with nitrous oxide in oxygen and isoflurane.. Duration Surgery and inpatient period. Concurrent medication/care: Preoperatively medicated with lormetazepam, diclofenac and ranitidine 1.5 hours before surgery. Postoperatively people were given patient-controlled analgesia of parenteral morphine to be used as rescue analgesia until the second postoperative day.. Indirectness: No indirectness (n=30) Intervention 2: General - General anaesthesia with nerve block. Neural blocks were inserted before induction of anaesthesia. Epidural catheter utilised with an infusion of bupivacaine commenced after surgical incision.General anaesthesia was induced with propofol and fentanyl. Anaesthesia was maintained with nitrous oxide in oxygen and isoflurane.. Duration Surgery and inpatient period. Concurrent medication/care: Preoperatively medicated with lormetazepam, diclofenac and ranitidine 1.5 hours before surgery. Postoperatively people were given patient-controlled analgesia of parenteral morphine to be used as rescue analgesia until the second postoperative day.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GENERAL AND REGIONAL ANAESTHESIA versus GENERAL ANAESTHESIA WITH NERVE BLOCK Protocol outcome 1: Postoperative pain at within 30 days - Actual outcome: No pain on attempted movement at In recovery ; Group 1: 23/29, Group 2: 16/30 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: Pain ; Group 1 Number missing: 1, Reason: failed epidural; 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; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Dimaculangan 2019[55]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and followed until discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with primary osteoarthritis who are scheduled for elective unilateral primary TKA
Exclusion criteria	Weight >120kg, inability to understand pain scales or the use of a PCA device, history of chronic opioid consumption, chronic pain syndromes, allergy to local anaesthetics or opioids, previous lower extremity vascular surgery, peripheral neuropathy
Age, gender and ethnicity	Age - Mean (SD): 65 (8), 62 (11). Gender (M:F): 9/35. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (II-III).
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacaine. LIA using ropivacaine, epinephrine, ketorlac, morphine, and saline. . Duration Surgery until discharge. Concurrent medication/care: Continuous femoral nerve block utilised. Postoperative PCA using morphine. . Indirectness: No indirectness (n=21) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthesia using bupivacaine. Sham LIA using saline. . Duration Surgery until discharge. Concurrent medication/care: Continuous femoral nerve block utilised. Postoperative PCA using morphine. . Indirectness: No indirectness
Funding	Funding not stated (It was stated that 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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain at rest at Postoperative day 1; Group 1: mean 37.6 (SD 35.3); n=23, Group 2: mean 35.2 (SD 27.9); n=21; VAS 0-100 Top=High

is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Postoperative use of analgesia at as reported - Actual outcome: PCA morphine consumption at 48 hours after surgery; Group 1: mean 41.5 mg (SD 32.9); n=23, Group 2: mean 52.6 mg (SD 40.6); n=21 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 5.1 days (SD 2.1); n=23, Group 2: mean 3.8 days (SD 1.6); n=21 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at within 90 days; Quality of life at within 30 days; Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Goyal 2013[86]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 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	Adults undergoing primary, unilateral TKA for degenerative arthritis.
Exclusion criteria	Medical history included peripheral inflammatory disease, hypersensitivity to opiates, fibromyalgia, Paget's disease, allergy or intolerance to local anesthetic medications, sleep apnea (contraindication for the intrathecal opioid), and chronic opioid use possibly leading to opioid tolerance or opioid-induced hyperalgesia, body mass index (BMI) greater than 40 kg/m2, American Society of Anesthesiologists score of 4 or higher, or any major renal (potential contraindication to nonsteroidal antiinflammatory drugs) or liver (potential contraindication to acetaminophen) impairment were excluded as well.
Recruitment/selection of patients	June 2919 to May 2011.
Age, gender and ethnicity	Age - Mean (SD): 63 and 65. Gender (M:F): 65/85. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia with bupivacaine. LIA immediately after the operation using bupivacaine. Elastomeric pump released fluid at a constant rate until 2nd postoperative day.. Duration Surgery and in-hospital period. Concurrent medication/care: Standard analgesia protocol was used for all people. Preoperative oral doses of acetaminophen, pregabalin, and celecoxib. Postoperative oral doses of acetaminophen, pregabalin and IV ketorolac every 6 hours. People were offered narcotic medication as necessary to alleviate breakthrough pain not managed through the scheduled drug administration.. Indirectness: No indirectness (n=80) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthesia with bupivacaine. LIA placebo using saline.. Duration Surgery and in-hospital period. Concurrent medication/care: Standard analgesia protocol was used for all people. Preoperative oral doses of acetaminophen, pregabalin, and celecoxib.

	Postoperative oral doses of acetaminophen, pregabalin and IV ketorolac every 6 hours. People were offered narcotic medication as necessary to alleviate breakthrough pain not managed through the scheduled drug administration.. Indirectness: No indirectness
Funding	Funding not stated (It was stated there were no conflicts of interest amongst the authors)

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: Pain at Postoperative day 1; Group 1: mean 30.3 (SD 23.11); n=75, Group 2: mean 39.59 (SD 23.11); n=75; VAS 0-100 Top=High is poor outcome
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 not specified; Group 1 Number missing: 5, Reason: Four patients were excluded postoperatively because of leaking from the catheter site during physical therapy requiring early removal, and six patients were excluded for having comorbidities that contraindicated spinal anesthesia and/or Duramorph as part of their anesthesia.; Group 2 Number missing: 5, Reason: Four patients were excluded postoperatively because of leaking from the catheter site during physical therapy requiring early removal, and six patients were excluded for having comorbidities that contraindicated spinal anesthesia and/or Duramorph as part of their anesthesia.

Protocol outcome 2: Thromboembolic complications at within 90 days
- Actual outcome: Pulmonary embolism at Unclear; Group 1: 1/75, Group 2: 0/75
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 not specified; Group 1 Number missing: 5, Reason: Four patients were excluded postoperatively because of leaking from the catheter site during physical therapy requiring early removal, and six patients were excluded for having comorbidities that contraindicated spinal anesthesia and/or Duramorph as part of their anesthesia.; Group 2 Number missing: 5, Reason: Four patients were excluded postoperatively because of leaking from the catheter site during physical therapy requiring early removal, and six patients were excluded for having comorbidities that contraindicated spinal anesthesia and/or Duramorph as part of their anesthesia.

Protocol outcome 3: Hospital readmissions at within 30 days
- Actual outcome: Reoperations at Unclear; Group 1: 3/75, Group 2: 5/75
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 not specified; Group 1 Number missing: 5, Reason: Four patients were excluded postoperatively because of leaking from the catheter site during physical therapy requiring early removal, and six patients were excluded for having comorbidities that contraindicated spinal anesthesia and/or Duramorph as part of their anesthesia.; Group 2 Number missing: 5, Reason: Four patients were excluded postoperatively because of leaking from the catheter site during physical therapy requiring early removal, and six patients were excluded for having comorbidities that contraindicated spinal anesthesia and/or Duramorph as part of their anesthesia.
- Actual outcome: Manipulation under anesthesia for postoperative stiffness at 6 weeks after the operation; Group 1: 3/75, Group 2: 3/75
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 not specified; Group 1 Number missing: 5, Reason: Four patients were excluded postoperatively because of leaking from the catheter site during physical therapy requiring early removal, and six patients were excluded for having comorbidities that contraindicated spinal anesthesia and/or Duramorph as part of their anesthesia.; Group 2 Number missing: 5, Reason: Four patients were excluded postoperatively because of leaking from the catheter site during physical therapy requiring early removal, and six patients were excluded for having comorbidities that contraindicated spinal anesthesia and/or Duramorph as part of their anesthesia. Protocol outcome 4: Postoperative use of analgesia at as reported - Actual outcome: Narcotic consumption at Postoperative day 1; Group 1: mean 11.73 mg (SD 12.47); n=75, Group 2: mean 11.84 mg (SD 12.47); 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: Serious indirectness, Comments: 1 person in the experimental group whose consumption was very high was excluded from analysis. ; Baseline details: ASA not specified; Group 1 Number missing: 5, Reason: Four patients were excluded postoperatively because of leaking from the catheter site during physical therapy requiring early removal, and six patients were excluded for having comorbidities that contraindicated spinal anesthesia and/or Duramorph as part of their anesthesia.; Group 2 Number missing: 5, Reason: Four patients were excluded postoperatively because of leaking from the catheter site during physical therapy requiring early removal, and six patients were excluded for having comorbidities that contraindicated spinal anesthesia and/or Duramorph as part of their anesthesia.	
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; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Grosso 2018[89]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=155)
Countries and setting	Conducted in USA
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 undergoing elective unilateral primary TKA
Exclusion criteria	Contraindications to spinal anaesthesia or nerve block, allergic to bupivacaine.
Age, gender and ethnicity	Age - Mean (SD): 69, 73, 71. Gender (M:F): 51/99. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness

Interventions	(n=54) Intervention 1: Regional - Regional anaesthesia with nerve block and local infiltration analgesia (during or after surgery). Spinal anaesthesia. Adductor canal block (ACB) using bupivacaine. LIA performed intraoperatively using bupivacaine at two points during surgery. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, oxycodone, celecoxib, and gabapentin. Postoperative medication: acetaminophen, ketorolac, gabapentin, oral opioids as needed, IV hydromorphone. . Indirectness: No indirectness (n=55) Intervention 2: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia. Adductor canal block (ACB) using bupivacaine. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, oxycodone, celecoxib, and gabapentin. Postoperative medication: acetaminophen, ketorolac, gabapentin, oral opioids as needed, IV hydromorphone. . Indirectness: No indirectness (n=54) Intervention 3: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia. LIA performed intraoperatively using bupivacaine at two points during surgery. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, oxycodone, celecoxib, and gabapentin. Postoperative medication: acetaminophen, ketorolac, gabapentin, oral opioids as needed, IV hydromorphone. . Indirectness: No indirectness
Funding	Academic or government funding (Partially funded by Orthopaedic Research and Education Foundation (OREF))

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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain at Postoperative day 1; Group 1: mean 3 (SD 2.1); n=51, Group 2: mean 3.9 (SD 2.3); n=53; VAS 0-10 Top=High is poor outcome
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 not detailed; Group 1 Number missing: 3, Reason: Received general anaesthesia; Group 2 Number missing: 2, Reason: Received general anaesthesia

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Total opioid consumption at Postoperative day 3; Group 1: mean 98 mg (SD 62); n=51, Group 2: mean 131 mg (SD 74); n=53
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 not detailed; Group 1 Number missing: 3, Reason: Received general anaesthesia; Group 2 Number missing: 2, Reason: Received general anaesthesia

Protocol outcome 3: Length of stay at .
- Actual outcome: Length of stay at .; Group 1: mean 2.5 days (SD 2.1); n=51, Group 2: mean 2.9 days (SD 1.5); n=53
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 not detailed; Group 1 Number missing: 3, Reason: Received general anaesthesia; Group 2 Number missing: 2, Reason: Received general anaesthesia

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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain at Postoperative day 1; Group 1: mean 3 (SD 2.1); n=51, Group 2: mean 3.8 (SD 2.4); n=51; VAS 0-10 Top=High is poor outcome
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 not detailed; Group 1 Number missing: 2, Reason: Received general anaesthesia; Group 2 Number missing: 2, Reason: Received general anaesthesia

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Total opioid consumption at Postoperative day 3; Group 1: mean 98 mg (SD 62); n=51, Group 2: mean 100 mg (SD 62); n=51
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 not detailed; Group 1 Number missing: 2, Reason: Received general anaesthesia; Group 2 Number missing: 2, Reason: Received general anaesthesia

Protocol outcome 3: Length of stay at .
- Actual outcome: Length of stay at .; Group 1: mean 2.5 days (SD 2.1); n=51, Group 2: mean 2.5 days (SD 1.2); n=51
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 not detailed; Group 1 Number missing: 2, Reason: Received general anaesthesia; Group 2 Number missing: 2, Reason: Received general anaesthesia

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 pain at within 30 days
- Actual outcome: Pain at Postoperative day 1; Group 1: mean 3.8 (SD 2.4); n=51, Group 2: mean 3.9 (SD 2.3); n=53; VAS 0-10 Top=High is poor outcome
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 not detailed; Group 1 Number missing: 3, Reason:

Received general anaesthesia; Group 2 Number missing: 2, Reason: Received general anaesthesia Protocol outcome 2: Postoperative use of analgesia at as reported - Actual outcome: Total opioid consumption at Postoperative day 3; Group 1: mean 100 mg (SD 62); n=51, Group 2: mean 131 mg (SD 74); n=53 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 not detailed; Group 1 Number missing: 3, Reason: Received general anaesthesia; Group 2 Number missing: 2, Reason: Received general anaesthesia Protocol outcome 3: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 2.5 days (SD 1.2); n=51, Group 2: mean 2.9 days (SD 1.5); n=53 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 not detailed; Group 1 Number missing: 3, Reason: Received general anaesthesia; Group 2 Number missing: 2, Reason: Received general anaesthesia	
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; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Han 2007[95]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in South Korea
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 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	People scheduled for primary TKA
Exclusion criteria	Over 80 years old, body weight over 100kg, ASA IV and higher, alcohol of narcotics abuse, hypersensitivity to morphine or local anaesthesia.
Recruitment/selection of patients	December 2005 to February 2006.
Age, gender and ethnicity	Age - Mean (range): 69 (58-78), 68 (52-79), 67 (52-78). Gender (M:F): 12/78. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: ASA grade I or II (I-II).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using tetracaine. LIA using ropivacaine, epinephrine and morphine injected into 10 different areas around the synovium. . Duration Surgery and 24 hours PCA. Concurrent medication/care: PCA via epidural infusion pump using ropivacaine, sufentanyl, nalaxone and saline. . Indirectness: Serious indirectness; Indirectness comment: Included morphine in LIA on top of local anaesthetics (n=30) Intervention 2: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using tetracaine. LIA using ropivacaine and epinephrine injected into 10 different areas around the synovium. . Duration Surgery and 24 hours PCA. Concurrent medication/care: PCA via epidural infusion pump using ropivacaine, sufentanyl, nalaxone and saline. . Indirectness: No indirectness (n=30) Intervention 3: Regional - Regional anaesthesia. Spinal anaesthesia using tetracaine.. Duration Surgery and 24 hours PCA. Concurrent medication/care: PCA via epidural infusion pump using ropivacaine, sufentanyl, nalaxone and saline. . 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): MORPHINE versus REGIONAL ANAESTHESIA

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain without exercise at 2 hours after surgery; Group 1: mean 2.3 (SD 3.1); n=30, Group 2: mean 1.8 (SD 3.1); n=30; VAS 0-10 Top=High is poor outcome
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:N/A ; Group 2 Number missing: N/A

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Use of PCA at First postoperative day; Group 1: mean 29.7 mg (SD 10.6); n=30, Group 2: mean 33.8 mg (SD 7.4); n=30
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: N/A ; Group 2 Number missing: N/A

Protocol outcome 3: Nausea at within 30 days
- Actual outcome: Nausea at Within 48 hours of surgery; Group 1: 14/30, Group 2: 12/30
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: N/A ; Group 2 Number missing: N/A

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: Pain without exercise at 2 hours after surgery; Group 1: mean 1.7 (SD 2.7); n=30, Group 2: mean 1.8 (SD 3.1); n=30; VAS 0-10 Top=High is poor outcome
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: N/A ; Group 2 Number missing: N/A

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Use of PCA at First postoperative day; Group 1: mean 32.7 mg (SD 11); n=30, Group 2: mean 33.8 mg (SD 7.4); n=30
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: N/A; Group 2 Number missing: N/A

Protocol outcome 3: Nausea at within 30 days
- Actual outcome: Nausea at Within 48 hours of surgery; Group 1: 12/30, Group 2: 12/30
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: N/A; Group 2 Number missing: N/A	
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; Length of stay at .; Mobilisation within 24 hours after surgery at .

Study	Harsten 2013[98]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Sweden; Setting: Department of Orthopaedic Surgery, Ha¨ssleholm Hospital, Sweden. September 2011 to June 2012
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 months 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 undergoing TKA. Inclusion criteria: ASA I–III, able to understand the given information, Between 45 and 85 years of age,
Exclusion criteria	Previous major knee surgery to the same knee, obesity (BMI>35), rheumatoid arthritis, immunological depression, and allergy to any of the drugs used in this study, taking opioids or steroids, a history of stroke or psychiatric disease that could affect the perception of pain.
Age, gender and ethnicity	Age - Mean (SD): 68 (7) and 67 (7). Gender (M:F): 59/61. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness

Interventions	(n=60) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacaine. Towards the end of surgery, all subjects received infiltration of local anaesthetic (epinephrine and ropivacaine) in the perisurgical area. . Duration Surgery in hospital period. Concurrent medication/care: Light sedation using propofol during surgery.Patient controlled analgesia (PCA) delivering IV morphine used for for postoperative pain medication during the first postoperative 24 h.. Indirectness: No indirectness (n=60) Intervention 2: General - General anaesthesia with local infiltration analgesia (during or after procedure). General anaesthesia via target controlled infusion (TCI) with propofol and remifentanil. Towards the end of surgery, all subjects received infiltration of local anaesthetic (epinephrine and ropivacaine) in the perisurgical area. . Duration Surgery in hospital period. Concurrent medication/care: Patient controlled analgesia (PCA) delivering IV morphine used for for postoperative pain medication during the first postoperative 24 h.. Indirectness: No indirectness
Funding	Academic or government funding (The study was supported with institutional grants.)

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

Protocol outcome 1: Thromboembolic complications at within 90 days
- Actual outcome: Pulmonary embolism at Unclear; Group 1: 1/60, Group 2: 1/60
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 ; Baseline details: Regional group had slightly worse ASA ratings; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Length of stay at .
- Actual outcome: Length of stay at .; Group 1: mean 52 hours (SD 9.74); n=60, Group 2: mean 46 hours (SD 9.74); n=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 ; Baseline details: Regional group had slightly worse ASA ratings; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Nausea at within 30 days
- Actual outcome: Nausea at Morning on day after surgery; Group 1: 0/60, Group 2: 17/60
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 ; Baseline details: Regional group had slightly worse ASA ratings; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome: Nausea at Afternoon on day after surgery; Group 1: 0/60, Group 2: 0/60 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 ; Baseline details: Regional group had slightly worse ASA ratings; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Mobilisation within 24 hours after surgery at . - Actual outcome: Able to walk 5 metres at 24 hours after surgery; Group 1: 59/60, 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 ; Baseline details: Regional group had slightly worse ASA ratings; 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; Hospital readmissions at within 30 days; Postoperative use of analgesia at as reported

Study	Hinarejos 2016[104]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=101)
Countries and setting	Conducted in Spain
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 months 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 knee osteoarthritis who are 40-85 years old.
Exclusion criteria	Allergy to study medications, contraindications to or failure of spinal anaesthesia, psychiatric disease, polyneuropathy, weight under 60kg, treatment with skin patches of morphic derivatives, treatment with antiarrhythmic drugs class III, treatment with portent CYP1A2 inhibitors, no withdrawal of NSAIDs or corticosteroids 24 hours before surgery, known drug or alcohol abuse, inflammatory arthritis, previous major surgery on operated knee.
Recruitment/selection of patients	September 2013 to June 2014.
Age, gender and ethnicity	Age - Mean (SD): 72 (7). Gender (M:F): 25/75. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacaine. LIA using ropivacaine, epinephrine, and ketorolac in the soft tissues around the join before closure. . Duration Surgery and in-hospital period. . Concurrent medication/care: Intraoperative conscious sedation not restricted. Femoral and sciatic nerve blocks postoperatively using bupivacaine and adrenaline. Postoperative analgesia via paracetamol and dexketoprofen. Rescue medication using tramadol or morphine where required. . Indirectness: No indirectness (n=50) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthesia using bupivacaine. . Duration Surgery and in-hospital period. . Concurrent medication/care: Intraoperative conscious sedation not restricted. Femoral and sciatic nerve blocks postoperatively using bupivacaine and adrenaline. Postoperative analgesia via paracetamol and dexketoprofen. Rescue medication using tramadol or

	morphine where required. . Indirectness: No indirectness
Funding	Funding not stated (It was stated that the authors had 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

Protocol outcome 1: Thromboembolic complications at within 90 days
- Actual outcome: Pulmonary embolism at Postoperative period; Group 1: 0/50, Group 2: 1/50
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: Unclear about distribution of ASA scores; Group 1 Number missing: 1; Group 2 Number missing: 0

Protocol outcome 2: Hospital readmissions at within 30 days
- Actual outcome: Stiffness requiring arthroscopic arthrolysis at Postoperative period; Group 1: 0/50, Group 2: 2/50
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: Unclear about distribution of ASA scores; Group 1 Number missing: 1; Group 2 Number missing: 0

Protocol outcome 3: Postoperative use of analgesia at as reported
- Actual outcome: Morphine used as rescue medication at On postoperative day 1; Group 1: 18/50, Group 2: 23/50
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: Unclear about distribution of ASA scores; Group 1 Number missing: 1; 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; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Kastelik 2019[134]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Germany; Setting: Charite – Universitatsmedizin Berlin, Campus Charite Mitte, Germany
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 5 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults undergoing elective, primary TKA under general anaesthesia
Exclusion criteria	Heart insufficiency, liver insufficiency, evidence of diabetic polyneuropathy, severe obesity, pregnancy, patients in police custody, participation in another interventional RCT, chronic opioid therapy for more than 3 months before scheduled surgery and allergy to any of the medications required for anaesthesia.
Age, gender and ethnicity	Age - Mean (SD): 66.6 (10). Gender (M:F): 23/17. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: General - General anaesthesia with nerve block. Single shot sciatic nerve block using ropivacaine and adductor canal block using prilocaine. General anaesthesia was maintained with propofol or sevoflurane and bolus doses of fentanyl or continuous administration of remifentanil depending on the person's requirements in accordance with the local SOP.. Duration Surgery and until hospital discharge. Concurrent medication/care: Patient-controlled analgesia device was programmed and connected to the saphenous nerve catheter in the postanaesthesia care unit for postoperative pain management (ropivacaine 0.2%, infusion at 6 ml with lock-out time 30 min, 4 ml bolus dose on demand). Postoperatively, all people were treated for pain with oral tramadol (sustained release) 100mg twice daily with acute rescue pain medication of oral morphine 10mg (maximum six times a day). In addition, all people received combined cyclo-oxygenase inhibition with oral ibuprofen 600mg three times daily and dipyrone 1000mg three times daily. Rescue adductor canal catheter placement was available in LIA patients with insufficient pain control.. Indirectness: No indirectness (n=20) Intervention 2: General - General anaesthesia with local infiltration analgesia (during or after procedure). General anaesthesia was maintained with propofol or sevoflurane and bolus doses of fentanyl or continuous administration of remifentanil depending on the person's requirements in accordance with the local SOP. Periarticular infiltration with local anaesthetics around knee joint capsule including the posterior

	joint structures, periarticular soft tissue and subcutaneous soft tissue. Infiltration was performed after the implantation of the femoral and tibial component before positioning the liner following a routinely used protocol with 150 ml of ropivacaine.. Duration Surgery and until hospital discharge. Concurrent medication/care: Patient-controlled analgesia device was programmed and connected to the saphenous nerve catheter in the postanaesthesia care unit for postoperative pain management (ropivacaine 0.2%, infusion at 6 ml with lock-out time 30 min, 4 ml bolus dose on demand). Postoperatively, all people were treated for pain with oral tramadol (sustained release) 100mg twice daily with acute rescue pain medication of oral morphine 10mg (maximum six times a day). In addition, all people received combined cyclo-oxygenase inhibition with oral ibuprofen 600mg three times daily and dipyrone 1000mg three times daily. Rescue adductor canal catheter placement was available in LIA patients with insufficient pain control.. Indirectness: No indirectness
Funding	No funding (Financial support and sponsorship: none)
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: Length of stay at . - Actual outcome: Time to discharge at .; Group 1: mean 6.2 days (SD 0.5); n=20, Group 2: mean 6.3 days (SD 0.7); n=20 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: Mobilised at 31 hours after surgery; Group 1: 20/20, Group 2: 20/20 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; Postoperative use of analgesia at as reported; Nausea at within 30 days days

Study	Kayupov 2018[135]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=145)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery until discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis who are scheduled to undergo primary unilateral TKA
Exclusion criteria	BMI>40, history of drug or alcohol abuse, taking opioids for pain medications for longer than 6 months, contraindication to spinal or general anaesthesia, not able to ambulate at baseline.
Recruitment/selection of patients	January 2015 to March 2016.
Age, gender and ethnicity	Age - Mean (SD): 64, 63, 60. Gender (M:F): 67/65. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Regional - Regional anaesthesia with nerve block. Spinal anaesthetic. Continuous adductor canal block (CACB) . Duration Surgery until discharge. Concurrent medication/care: Premedication: celecoxib, pregabalin, scopolamine transdermal patch. Intraoperatively people received dexamethasone, ketorolac, acetaminophen, and ondansetron. Postoperative medication: oxycontin, hydrocodone/acetaminophen, celecoxib, and pregabalin. . Indirectness: No indirectness (n=48) Intervention 2: General - General anaesthesia with nerve block. General anaesthesia. Continuous adductor canal block (CACB) . Duration Surgery until discharge. Concurrent medication/care: Premedication: celecoxib, pregabalin, scopolamine transdermal patch. Intraoperatively people received dexamethasone, ketorolac, acetaminophen, and ondansetron. Postoperative medication: oxycontin, hydrocodone/acetaminophen, celecoxib, and pregabalin. . Indirectness: No indirectness (n=51) Intervention 3: Regional - Regional anaesthesia. Combined spinal/epidural anaesthesia. . Duration Surgery until discharge. Concurrent medication/care: Premedication: celecoxib, pregabalin, scopolamine transdermal patch. Intraoperatively people received dexamethasone, ketorolac, acetaminophen, and ondansetron. Postoperative medication: oxycontin, hydrocodone/acetaminophen, celecoxib, and pregabalin.

	. Indirectness: No indirectness
Funding	Academic or government funding ("Departmental funding")

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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain at Postoperative day 1; Group 1: mean 2.9 (SD 1.8); n=41, Group 2: mean 3.3 (SD 2.2); n=47; Defence and Veterans Pain Rating Scale 0-10 Top=High is poor outcome
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: 5; Group 2 Number missing: 1

Protocol outcome 2: Length of stay at .
- Actual outcome: Length of stay at .; Group 1: mean 51 hours (SD 16.28); n=41, Group 2: mean 53 hours (SD 37.57); n=47
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: 5; Group 2 Number missing: 1

Protocol outcome 3: Mobilisation within 24 hours after surgery at .
- Actual outcome: Ambulation distance at Postoperative day 1; Group 1: mean 235 feet (SD 142); n=41, Group 2: mean 218 feet (SD 126); n=47
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 1

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 Postoperative day 1; Group 1: mean 2.9 (SD 1.8); n=41, Group 2: mean 4.1 (SD 2.5); n=44; Defence and Veterans Pain Rating Scale 0-10 Top=High is poor outcome
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: 5; Group 2 Number missing: 7

Protocol outcome 2: Length of stay at .
- Actual outcome: Length of stay at .; Group 1: mean 51 hours (SD 16.28); n=41, Group 2: mean 59 hours (SD 23.32); n=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: 5; Group 2 Number missing: 7

Protocol outcome 3: Mobilisation within 24 hours after surgery at .

- Actual outcome: Ambulation distance at Postoperative day 1; Group 1: mean 235 feet (SD 142); n=41, Group 2: mean 146 feet (SD 116); n=44 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 7 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA versus GENERAL ANAESTHESIA WITH NERVE BLOCK Protocol outcome 1: Postoperative pain at within 30 days - Actual outcome: Pain at Postoperative day 1; Group 1: mean 4.1 (SD 2.5); n=44, Group 2: mean 3.3 (SD 2.2); n=47; Defence and Veterans Pain Rating Scale 0-10 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 1 Protocol outcome 2: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 59 hours (SD 23.32); n=44, Group 2: mean 53 hours (SD 37.57); n=47 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 1 Protocol outcome 3: Mobilisation within 24 hours after surgery at . - Actual outcome: Ambulation distance at Postoperative day 1; Group 1: mean 146 feet (SD 116); n=44, Group 2: mean 235 feet (SD 142); n=41 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 1	
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; Postoperative use of analgesia at as reported; Nausea at within 30 days

Study	Kim 2018[139]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=86)
Countries and setting	Conducted in USA; Setting: Single centre study.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with follow-up until discharge
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, with osteoarthritis who are scheduled for primary unilateral TKA. People must be able to speak English.
Exclusion criteria	Inability to follow study protocol, hepatic or renal insufficiency, scheduled for general anaesthesia, allergy or intolerance to any study medications, BMI >40, diabetes, ASA class IV, chronic gabapentin or pregabalin use, chronic opioid use, severe vagus deformity and flexion contracture.
Recruitment/selection of patients	March to October 2017.
Age, gender and ethnicity	Age - Mean (SD): 67 (8) and 68 (7). Gender (M:F): 33/53. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Regional - Regional anaesthesia with nerve block and local infiltration analgesia (during or after surgery). Combined spinal epidural anaesthetic using mepivacaine. LIA using bupivacaine, epinephrine, methylprednisoline, cefazolin, and saline. This was injected at 2 times during the surgery. ACB and IPACK blocks using bupivacaine. . Duration Surgery until discharge. Concurrent medication/care: Peroperative: meloxicam and oxycodone. Sedation via midazolam and propofol. Fentanyl given at anesthesiologist's discretion. . Indirectness: No indirectness (n=43) Intervention 2: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Combined spinal epidural anaesthetic using mepivacaine. LIA using bupivacaine, epinephrine, methylprednisoline, cefazolin, and saline. This was injected at 2 times during the surgery.. Duration Surgery until discharge. Concurrent medication/care: Peroperative: meloxicam and oxycodone. Sedation via midazolam and propofol. Fentanyl given at anesthesiologist's discretion. . Indirectness: No indirectness
Funding	Funding not stated (It was stated that authors had no conflicts of interest)

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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain at rest at Postoperative day 0; Group 1: mean 0.8 (SD 1.1); n=43, Group 2: mean 3.5 (SD 2.4); n=43; Numerical Rating Scale 0-10 Top=High is poor outcome
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: Postoperative use of analgesia at as reported
- Actual outcome: Total opioid consumption at 0-24 hours after surgery; Group 1: mean 40.6 mg (SD 32.1); n=43, Group 2: mean 69.1 mg (SD 79.9); n=43
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 3: Mobilisation within 24 hours after surgery at .
- Actual outcome: Distance walked at Postoperative day 1; Group 1: mean 87.7 feet (SD 46.2); n=43, Group 2: mean 81.1 feet (SD 61); n=42
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: Unclear

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

Study	Mcnamee 2001[176]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 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	Adults under 86 years of age, from 40kg-95kg, no contraindications to regional anaesthesia and ASA I-III scheduled to undergo primary unilateral TKA.
Exclusion criteria	Not detailed
Age, gender and ethnicity	Age - Mean (range): 70 (54-84), 69 (58-83), 68 (47-83). Gender (M:F): 26/48. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Regional - Regional anaesthesia. Spinal anaesthesia using bupivacaine. Nerve blockade area dressed and prepared appropriately though no nerve block used.. Duration Surgery and hospital period. . Concurrent medication/care: Premedicated with diazepam. Propofol used for sedation. Postoperative PCA with morphine utilised. . Indirectness: No indirectness (n=25) Intervention 2: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia using bupivacaine. Femoral and sciatic nerve block using bupivacaine. . Duration Surgery and hospital period. . Concurrent medication/care: Premedicated with diazepam. Propofol used for sedation. Postoperative PCA with morphine utilised. . Indirectness: No indirectness (n=25) Intervention 3: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia using bupivacaine. Femoral and sciatic nerve block using bupivacaine. . Duration Surgery and hospital period. . Concurrent medication/care: Premedicated with diazepam. Propofol used for sedation. Postoperative PCA with morphine utilised. . 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; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Milani 2015[181]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Italy
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery until discharge from hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 71 (8)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults over 60 years of age, with primary knee osteoarthritis, who are scheduled for primary unilateral TKA.
Exclusion criteria	Cognitive impairment, sensory or motor disorders in the operated limb, known allergy to study medications, history of drug abuse.
Recruitment/selection of patients	January to December 2013.
Age, gender and ethnicity	Age - Mean (SD): . Gender (M:F): Precise numbers unclear thuogh 1:2 ratio was stated. Ethnicity: Not detailed
Further population details	1. Age: 60 years or older (Over 60 years of age.). 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Single shot spinal anaesthesia using bupivacaine. Periarticular ropivacaine administered before would closure. . Duration Surgery until discharge. Concurrent medication/care: Oral and IV multimodal analgesia: oxycodone/naloxone prior to surgery and post surgery, methylprednisolone prior to surgery, IM ketorolac utilised when people report high pain after surgery. Indirectness: No indirectness (n=32) Intervention 2: Regional - Regional anaesthesia. Single shot spinal anaesthesia using bupivacaine. Periarticular saline administered before would closure. . Duration Surgery until discharge. Concurrent medication/care: Oral and IV multimodal analgesia: oxycodone/naloxone prior to surgery and post surgery, methylprednisolone prior to surgery, IM ketorolac utilised when people report high pain after surgery. Indirectness: No indirectness
Funding	Funding not stated (It was stated that the authors have 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; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Mitchell 1991[185]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=72)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with osteoarthritis or rheumatoid arthritis who are over 40 years of age and scheduled for primary TKA. They must have normal haematological, renal and nutritional parameters.
Exclusion criteria	Previous surgery to the affected knee, malignancy, history of DVT or PE.
Recruitment/selection of patients	January 1987 to June 1988. Consecutive patients.
Age, gender and ethnicity	Age - Mean (range): 64 (38-84). Gender (M:F): 45/27. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Regional - Regional anaesthesia. Epidural anaesthesia. . Duration Surgery and follow-up until discharge. Concurrent medication/care: Premedication: aspirin for male people and warfarin for female people. Postoperative medication unclear. . Indirectness: No indirectness (n=38) Intervention 2: General - General anaesthesia. General anaesthesia: sodium thiopental used for induction. Adjunctive IV medications used. . Duration Surgery and follow-up until discharge. Concurrent medication/care: Premedication: aspirin for male people and warfarin for female people. Postoperative medication unclear. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA versus GENERAL ANAESTHESIA

Protocol outcome 1: Thromboembolic complications at within 90 days
- Actual outcome: DVT or PE at Before discharge; Group 1: 12/34, Group 2: 10/38
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 or equivalent not reported; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at within 90 days; Quality of life at within 30 days; Postoperative pain at within 30 days; Postoperative neurocognitive decline at within 30 days; Hospital readmissions at within 30 days; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Moghtadaei 2014[186]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Iran; Setting: Single centre study on orthopaedic ward in Rasoul Akram Hospital, Tehran, Iran.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months 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, aged 20 to 85 years old, ASA I-III, normal preoperative mobility, scheduled for TKA.
Exclusion criteria	Neuropathic pain or sensory disorders of the leg being operated, failed spinal anesthesia, therefore conversed to general anesthesia, a medical history showing previous operations on the suffering knee, allergy to the medicine used in the study, BMI > 40, diseases of kidney, heart or liver, joint inflammatory disease, chronic pain, disorders resulting in bleeding, such as GI bleeding.
Age, gender and ethnicity	Age - Mean (SD): 67 (7) and 64 (7). Gender (M:F): 25/11. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anesthesia using bupivacaine hydrochloride. LIA using ropivacaine, ketorolac, and epinephrine in 3 syringes utilised at 3 points during surgery.. Duration Surgery and in-hospital period. Concurrent medication/care: Premedication: midazolam was administered. Postoperative oral acetaminophen, Ibuprofen, and ranitidine administered. Rescue IV morphine used on request. Pain was controlled after 48 hours only with acetaminophen and oral tramadol.. Indirectness: No indirectness (n=20) Intervention 2: Regional - Regional anaesthesia with nerve block. Spinal anesthesia using bupivacaine hydrochloride. Femoral nerve block using ropivacaine.. Duration Surgery and in-hospital period. Concurrent medication/care: Premedication: midazolam was administered. Postoperative oral acetaminophen, Ibuprofen, and ranitidine administered. Rescue IV morphine used on request. Pain was controlled after 48 hours only with acetaminophen and oral tramadol.. Indirectness: No indirectness
Funding	Academic or government funding (Funded by Iran University of Medical Sciences Thesis grants)

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: Hospital readmissions at within 30 days
- Actual outcome: Readmission for irrigation, debridement and polythene exchange at 4 weeks after surgery; Group 1: 1/20, Group 2: 0/20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Nausea at within 30 days
- Actual outcome: Nausea at Unclear; Group 1: 0/20, Group 2: 1/20
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; Postoperative use of analgesia at as reported; Length of stay at .; Mobilisation within 24 hours after surgery at .

Study	Niemelainen 2014[201]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Finland; Setting: Surgery at 1 institution between March 2011 and March 2012
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 1 year follow-up
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 with osteoarthritis undergoing unilateral primary TKA
Exclusion criteria	Rheumatoid arthritis or other inflammatory diseases, BMI > 35, American Society of Anesthesiologists physical score > 3, renal dysfunction, allergy to any of the study drugs, previous high tibial osteotomy or previous osteosynthesis,> 15 degrees varus or valgus malalignment, physical, emotional, or neurological conditions that could compromise the patient's compliance to postoperative rehabilitation
Age, gender and ethnicity	Age - Mean (SD): 65 (5) and 64 (7). Gender (M:F): 27/29. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Single-shot spinal anesthesia induced using bupivacaine. Intraoperative LIA at 2 stages with a solution containing levobupivacaine, ketorolac and adrenaline.. Duration Surgery and in-hospital period. Concurrent medication/care: Premedication: oral paracetamol was given approximately 1 h before surgery. Postoperative medication: oral paracetamol, oral meloxicam, patient-controlled analgesia (PCA) with oxycodone. If the pain management was insufficient, a lumbar epidural catheter was inserted and levobupivacaine infusion was initiated as rescue analgesic, causing the patient to drop out from the study.. Indirectness: No indirectness (n=30) Intervention 2: Regional - Regional anaesthesia. Single-shot spinal anesthesia induced using bupivacaine. Intraoperative placebo LIA at 2 stages with a solution containing saline.. Duration Surgery and in-hospital period. Concurrent medication/care: Premedication: oral paracetamol was given approximately 1 h before surgery. Postoperative medication: oral paracetamol, oral meloxicam, patient-controlled analgesia (PCA) with oxycodone. If the pain management was insufficient, a lumbar epidural catheter was inserted and levobupivacaine infusion was initiated as rescue analgesic, causing the patient to drop out from the study.. Indirectness: No indirectness

Funding	Funding not stated (It was stated there were no "competing interests" declared)

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: Removed from the study: epidural analgesia due to intense postoperative pain at While in hospital; Group 1: 0/27, Group 2: 3/29
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Refused to participate; Group 2 Number missing: 1, Reason: Refused to participate

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Oxycodone via PCA at 0-6 hours after surgery; Group 1: mean 14 mg (SD 9.5); n=27, Group 2: mean 30 mg (SD 9.5); n=29
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Refused to participate; Group 2 Number missing: 1, Reason: Refused to participate

Protocol outcome 3: Nausea at within 30 days
- Actual outcome: Discontinued the study due to nausea at While in hospital; Group 1: 1/27, Group 2: 1/29
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Refused to participate; Group 2 Number missing: 1, Reason: Refused to participate

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; Length of stay at .; Mobilisation within 24 hours after surgery at .

Study	Rizk 2017[225]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Egypt
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery until discharge
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 scheduled for unilateral primary TKA
Exclusion criteria	History of septic arthritis or rheumatic disease, contraindications to regional or local anaesthetic, severe deformity of the knee, nerve affection of the leg, inability to understand the VAS, allergic to study medications.
Recruitment/selection of patients	September 2014 to October 2014.
Age, gender and ethnicity	Age - Mean (SD): 67 (7) and 69 (7). Gender (M:F): 25/50. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: General - General anaesthesia with local infiltration analgesia (during or after procedure). General anaesthesia. LIA using ropivacaine, ketorolac, epinephrine, and morphine. Intraarticular and periarticular injections used. . Duration Surgery until discharge. Concurrent medication/care: Unclear. Indirectness: No indirectness (n=34) Intervention 2: General - General anaesthesia with nerve block. General anaesthesia. Adductor canal block (ACB) and sciatic nerve block (SNB) using ropivacaine. . Duration Surgery until discharge. Concurrent medication/care: Unclear. 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: Postoperative use of analgesia at as reported

- Actual outcome: Opiate consumption at 48 hours after surgery; Group 1: mean 48.09 mg (SD 8.73); n=41, Group 2: mean 51.08 mg (SD 12.96); n=34 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: No ASA detailed; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 3.7 days (SD 0.54); n=41, Group 2: mean 4 days (SD 0.49); n=34 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: No ASA detailed; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Mobilisation within 24 hours after surgery at . - Actual outcome: Walk at least 10 meters at Postoperative day 1; Group 1: 40/41, Group 2: 33/34 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA 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; Nausea at within 30 days

Study	Rosen 2010[227]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in USA; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 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	Adults scheduled to have unilateral elective primary TKA.
Exclusion criteria	Known allergy or hypersensitivity to any local anesthetic of the amide type, had a history of prior infection or prior joint surgery (other than arthroscopy), required the use of a regional, spinal, or epidural anesthetic perioperatively, required the use of any MAOI, tryptalines, or imipramine type of antidepressant medication pre- and postoperatively, had evidence of abuse of legal or illicit drugs, consumed more than three alcoholic beverages per 24-hr period, had a history of chronic pain (e.g., fibromyalgia, complex regional pain syndrome, neuropathy), or had a history of cardiac disease requiring special monitoring or the use of antiarrhythmic medications.
Recruitment/selection of patients	People approached and were enrolled from a preoperative history and physical clinic.
Age, gender and ethnicity	Age - Mean (SD): 71. Gender (M:F): 12/36. 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=24) Intervention 1: General - General anaesthesia with local infiltration analgesia (during or after procedure). General anesthesia. LIA using ropivacaine injected into the intraarticular capsule after closure.. Duration Surgery and in-hospital period. Concurrent medication/care: IV pain medication given postoperatively. PCA with morphine utilised.. Indirectness: No indirectness (n=24) Intervention 2: General - General anaesthesia. General anesthesia. LIA placebo using saline injected into the intraarticular capsule after closure.. Duration Surgery and in-hospital period. Concurrent medication/care: Known allergy or hypersensitivity to any local anesthetic of the amide type, had a history of prior infection or prior joint surgery (other than arthroscopy), required the use of a regional, spinal, or epidural anesthetic perioperatively, required the use of any MAOI, tryptalines, or imipramine type of

	antidepressant medication pre- and postoperatively, had evidence of abuse of legal or illicit drugs, consumed more than three alcoholic beverages per 24-hr period, had a history of chronic pain (e.g., fibromyalgia, complex regional pain syndrome, neuropathy), or had a history of cardiac disease requiring special monitoring or the use of antiarrhythmic medications.. Indirectness: No indirectness
Funding	Funding not stated (It was stated that authors had no conflicts of interest)

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: Thromboembolic complications at within 90 days
- Actual outcome: Proximal DVT at Unclear; Group 1: 1/24, Group 2: 0/24
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 ACA; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Length of stay at .
- Actual outcome: Duration of the PACU stay at .; Group 1: mean 126 minutes (SD 55); n=24, Group 2: mean 142 minutes (SD 55); n=24
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 ACA; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Nausea at within 30 days
- Actual outcome: Nausea at Unclear; Group 1: 9/24, Group 2: 11/24
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 ACA; 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; Hospital readmissions at within 30 days; Postoperative use of analgesia at as reported; Mobilisation within 24 hours after surgery at .

Study	Runge 2016[230]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in Denmark; Setting: Silkeborg Regional Hospital, February 2014 to December 2014.
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	Adults over 50 years of age, ASA I-III, undergoing cemented unilateral primary TKA
Exclusion criteria	Inability to cooperate, linguistic barrier, immunosuppressive therapy, diabetes, lower limb neuropathy, daily intake of opioids, allergy to any study medication, alcohol or drugs abuse, intolerance to NSAIDs.
Age, gender and ethnicity	Age - Mean (SD): 71 (8), 73 (7), 70 (8). Gender (M:F): 39/38. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia using bupivacaine. Femoral triangle block and obturator nerve block using bupivacaine, epinephrine, clonidine, and dexamethasone. Sham LIA using saline. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, ibuprofen, and gabapentin. Propofol used for sedation at discretion of the anaesthetist. Postoperative medication: acetaminophen, ibuprofen, and gabapentin.. Indirectness: No indirectness (n=24) Intervention 2: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia using bupivacaine. Femoral triangle block using bupivacaine, epinephrine, clonidine, and dexamethasone. Sham obturator nerve block and LIA using saline. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, ibuprofen, and gabapentin. Propofol used for sedation at discretion of the anaesthetist. Postoperative medication acetaminophen, ibuprofen, and gabapentin.. Indirectness: No indirectness (n=27) Intervention 3: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacaine. Sham femoral triangle block and obturator nerve block using saline. Intraoperative LIA using ropivacaine, epinephrine, and ketorolac. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, ibuprofen, and gabapentin. Propofol

	used for sedation at discretion of the anaesthetist. Postoperative medication: acetaminophen, ibuprofen, and gabapentin.. Indirectness: No indirectness
Funding	Academic or government funding (Supported by the Moller Foundation,)
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; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Safa 2014[232]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Canada
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults 18-75 years old who are ASA I-III and scheduled for unilateral primary TKA
Exclusion criteria	Contraindicated to spinal anaesthesia or peripheral nerve blocks, allergy to any study medications, history of drug or alcohol abuse, chronic pain and on slow release preparations of an opioid, inability to comprehend pain scales, unable to use a PCA device, diabetes with impaired renal function, BMI >45.
Age, gender and ethnicity	Age - Mean (SD): 61. Gender (M:F): 64/46. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Regional - Regional anaesthesia with nerve block. Femoral nerve block using ropivacaine. Spinal anaesthesia using hypobaric bupivacaine. Placebo sciatic nerve block and LIA using saline. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, celecoxib, gabapentin. Sedation with midazolam at discretion of anesthetist. Intraoperative sedation using propofol. Postoperative medication: celecoxib, gabapentin, acetaminophen, IV PCA using oxycodone. . Indirectness: No indirectness (n=32) Intervention 2: Regional - Regional anaesthesia with nerve block and local infiltration analgesia (during or after surgery). Spinal anaesthesia using hypobaric bupivacaine. LIA using ropivacaine utilised at the end of the surgical procedure. Placebo nerve blocks using saline. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, celecoxib, gabapentin. Sedation with midazolam at discretion of anesthetist. Intraoperative sedation using propofol. Postoperative medication: celecoxib, gabapentin, acetaminophen, IV PCA using oxycodone. . Indirectness: No indirectness
Funding	Academic or government funding (Physician Services Incorporated Foundation (PSIF))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REGIONAL ANAESTHESIA WITH NERVE BLOCK AND LOCAL INFILTRATION ANALGESIA (DURING OR AFTER SURGERY) versus REGIONAL ANAESTHESIA WITH SINGLE NERVE BLOCK Protocol outcome 1: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 4.2 days (SD 0.99); n=32, Group 2: mean 4.3 days (SD 0.68); n=35 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 ASA details; 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; Postoperative use of analgesia at as reported; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Sakai 2013[236]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in Japan; Setting: Osaka University Medical Hospital.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 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	Adults who are ASA I-III scheduled for primary unilateral TKA
Exclusion criteria	Bilateral TKA, contraindications to analgesia techniques, allergy to any study medications, diabetes with sensory disorders, neurological disability, revision arthroplasty, chronic pain syndrome unrelated to knee pathology, chronic opioid use.
Recruitment/selection of patients	July 2010 to July 2011.
Age, gender and ethnicity	Age - Median (range): 73 (53-86) and 72 (48-84). Gender (M:F): 8/52. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: General - General anaesthesia with nerve block. Continuous femoral nerve block induced using ropivacaine. General anaesthesia induced using propofol. . Duration Surgery until discharge. Concurrent medication/care: No premedication given. Postoperatively people were given oral loxoprofen. Higher levels of pain were addressed with diclofenac suppositories and then IM pentazocine. IV fentanyl was available for further pain management if required. . Indirectness: No indirectness (n=33) Intervention 2: General and regional - General and regional anaesthesia. Epidural anaesthesia using ropivacaine. General anaesthesia induced using propofol. . Duration Surgery until discharge. Concurrent medication/care: No premedication given. Postoperatively people were given oral loxoprofen. Higher levels of pain were addressed with diclofenac suppositories and then IM pentazocine. IV fentanyl was available for further pain management if required. . Indirectness: No indirectness
Funding	Funding not stated

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

AND REGIONAL ANAESTHESIA Protocol outcome 1: Nausea at within 30 days - Actual outcome: Nausea/vomiting at Prior to discharge; Group 1: 4/30, Group 2: 6/30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Cancelled surgery, accidental catheter extraction, failure of catheter insertion. ; Group 2 Number missing: 3, Reason: Defective agreement document, 2 converted to another operative procedure. Protocol outcome 2: Mobilisation within 24 hours after surgery at . - Actual outcome: Ability to perform a straight-leg raise at Postoperative day 1; Group 1: 7/30, Group 2: 4/30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Cancelled surgery, accidental catheter extraction, failure of catheter insertion. ; Group 2 Number missing: 3, Reason: Defective agreement document, 2 converted to another operative procedure.	
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; Postoperative use of analgesia at as reported; Length of stay at .

Study	Sawhney 2016[244]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Canada
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with follow-up until discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults, ASA I-III, able to speak and read English who are scheduled for primary TKA.
Exclusion criteria	Contraindication to neuraxial or regional anaesthesia, allergy to local anaesthetics, chronic pain unrelated to knee joint, chronic opioid use, preexisting neuropathy involving the operative site.
Recruitment/selection of patients	May 2013 to February 2014.
Age, gender and ethnicity	Age - Mean (SD): 67 (10). Gender (M:F): 50/100. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: Regional - Regional anaesthesia with nerve block and local infiltration analgesia (during or after surgery). AC block using ropivacaine. Spinal anaesthesia using bupivacaine. LIA during surgery using ropivacaine, morphine, ketorolac, and saline. Infiltrated at 3 points during surgery. . Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, celecoxib, and gabapentin. Sedation with fentanyl and midazolam. PCA using hydromorphone. Acetaminophen, celecoxib, and gabapentin administered. . Indirectness: No indirectness (n=51) Intervention 2: Regional - Regional anaesthesia with nerve block. AC block using ropivacaine. Spinal anaesthesia using bupivacaine. Sham LIA during surgery using saline.. Duration Surgery until discharge. Concurrent medication/care: Premedication: acetaminophen, celecoxib, and gabapentin. Sedation with fentanyl and midazolam. PCA using hydromorphone. Acetaminophen, celecoxib, and gabapentin administered. . Indirectness: No indirectness (n=54) Intervention 3: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Sham AC block. Spinal anaesthesia using bupivacaine. LIA during surgery using ropivacaine, morphine, ketorolac, and saline. Infiltrated at 3 points during surgery. . Duration Surgery until discharge.

	Concurrent medication/care: Premedication: acetaminophen, celecoxib, and gabapentin. Sedation with fentanyl and midazolam. PCA using hydromorphone. Acetaminophen, celecoxib, and gabapentin administered. . Indirectness: No indirectness
Funding	Academic or government funding (New York General Hospital Exploration Fund)

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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain while walking at Postoperative day 1; Group 1: mean 3.3 (SD 2.82); n=50, Group 2: mean 6.2 (SD 2.82); n=46; Numerical Rating 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: No ASA score details; Group 1 Number missing: 4, Reason: 2 Withdrew, 2 surgery changed/cancelled; Group 2 Number missing: 5, Reason: 3 Withdrew, 2 surgery changed/cancelled

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: PCA hydromorphone at Total use after 48 hours; Group 1: mean 3.5 mg (SD 3.5); n=50, Group 2: mean 7 mg (SD 5.6); 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 ASA score details; Group 1 Number missing: 4, Reason: 2 Withdrew, 2 surgery changed/cancelled; Group 2 Number missing: 5, Reason: 3 Withdrew, 2 surgery changed/cancelled

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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain while walking at Postoperative day 1; Group 1: mean 3.3 (SD 3.2); n=50, Group 2: mean 4.9 (SD 3.2); n=49; Numerical Rating 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: No ASA score details; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: PCA hydromorphone at Total use after 48 hours; Group 1: mean 3.5 mg (SD 3.5); n=50, Group 2: mean 5 mg (SD 6.9); n=49
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 ASA score details; Group 1 Number missing: 0; Group 2 Number missing: 1

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 pain at within 30 days - Actual outcome: Pain while walking at Postoperative day 1; Group 1: mean 4.9 (SD 3.1); n=49, Group 2: mean 6.2 (SD 3.1); n=46; Numerical Rating 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: No ASA score details; Group 1 Number missing: 5, Reason: 3 Withdrew, 2 surgery changed/cancelled; Group 2 Number missing: 5, Reason: 3 Withdrew, 2 surgery changed/cancelled Protocol outcome 2: Postoperative use of analgesia at as reported - Actual outcome: PCA hydromorphone at Total use after 48 hours; Group 1: mean 5 mg (SD 6.9); n=49, Group 2: mean 7 mg (SD 5.6); 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 ASA score details; Group 1 Number missing: 5, Reason: 3 Withdrew, 2 surgery changed/cancelled; Group 2 Number missing: 5, Reason: 3 Withdrew, 2 surgery changed/cancelled	
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; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Sogbein 2017[267]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=82)
Countries and setting	Conducted in Canada; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People 18 to 85 years old, ASA I-III, who are scheduled for elective primary TKA.
Exclusion criteria	Psychiatric illness, cognitive impairment, narcotic dependency, extraneous sources of chronic pain, allergy to any study medications, contraindications to nerve blocks or multimodal analgesia, people in wheelchairs, when there is a language barrier.
Recruitment/selection of patients	June 2104 to June 2015. Recruited from 4 practices.
Age, gender and ethnicity	Age - Mean (SD): 68 (8) and 63 (9). Gender (M:F): 28/54. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia using hyperbaric bupivacaine. Motor sparing block using ropivacaine, epinephrine, morphine and ketorolac. This involved a adductor canal block (ACB), posterior pericapsular injection, and lateral femoral cutaneous nerve block. Sham LIA used. . Duration Surgery until discharge. Concurrent medication/care: Multimodal preoperative analgesia: acetaminophen, naproxen, gabapentin, granisetron. . Indirectness: No indirectness (n=41) Intervention 2: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using hyperbaric bupivacaine. LIA ropivacaine, epinephrine, morphine, and ketorolac. Injected at 3 points during surgery. Sham nerve blocks used. . Duration Surgery until discharge. Concurrent medication/care: Multimodal preoperative analgesia: acetaminophen, naproxen, gabapentin, granisetron. . Indirectness: No indirectness
Funding	No funding (Self funded study)
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: Thromboembolic complications at within 90 days - Actual outcome: Deep vein thrombosis at Prior to hospital discharge; Group 1: 0/35, Group 2: 1/35 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: 6; Group 2 Number missing: 6 Protocol outcome 2: Postoperative use of analgesia at as reported - Actual outcome: Oxycodone consumption at Within 12 hours of surgery; Group 1: mean 8.88 mg (SD 1.79); n=35, Group 2: mean 8.27 mg (SD 1.73); n=35 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: 6; Group 2 Number missing: 6 Protocol outcome 3: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 2.2 days (SD 1); n=35, Group 2: mean 2.4 days (SD 1); n=35 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: 6; Group 2 Number missing: 6	
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; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Stav 2017[273]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=107)
Countries and setting	Conducted in Israel
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with follow-up till postoperative day 2
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with osteoarthritis and ASA I–III who are scheduled to undergo elective TKA
Exclusion criteria	Previous TKA, TKA revision, TKA due to trauma or etiology other than osteoarthritis, under 18 years of age, presence of a local skin infection near the block injection site, allergy to local anesthetics, pre-existing peripheral neuropathy of the involved limb, demonstrated opioid dependency,23 coagulopathy, chronic pain syndrome, dementia, and/or an inability to comprehend the pain scale or use the PCA IV MO device.
Age, gender and ethnicity	Age - Mean (SD): 69 (7), 69 (9), 67 (7). Gender (M:F): 32/58. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: General - General anaesthesia. Total intravenous anesthesia with propofol and remifentanil.. Duration Surgery and in-hospital period. Concurrent medication/care: Premedication was IV fentanyl, midazolam, and local anes-thesia via injection of lidocaine. Postoperative pain control via PCA providing IV morphine. Indirectness: No indirectness (n=36) Intervention 2: General - General anaesthesia with nerve block. Total intravenous anesthesia with propofol and remifentanil. Single injection femoral nerve block using bupivacaine and adrenaline.. Duration Surgery and in-hospital period. Concurrent medication/care: Premedication was IV fentanyl, midazolam, and local anes-thesia via injection of lidocaine. Postoperative pain control via PCA providing IV morphine. Indirectness: No indirectness (n=35) Intervention 3: General - General anaesthesia with nerve block. Total intravenous anesthesia with propofol and remifentanil. Multiple nerve block: single injection into femoral, sciatic, obturator, and lateral femoral cutaneous nerve blocks using bupivacaine and adrenaline.. Duration Surgery and in-hospital period. Concurrent medication/care: Premedication was IV fentanyl, midazolam, and local anes-thesia via injection

	of lidocaine. Postoperative pain control via PCA providing IV morphine. Indirectness: No indirectness
Funding	Funding not stated (It was stated that authors had no conflicts of interest)

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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain at rest at Postoperative day 0; Group 1: mean 49 (SD 27); n=30, Group 2: mean 48.34 (SD 24); n=29; VAS 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain in nerve block group was lower; Group 1 Number missing: 6, Reason: 3 inappropriate follow-up, 1 sensitivity to adrenaline, 2 inability to use pain scale or PCA device; Group 2 Number missing: 7, Reason: 1 post-op treatment with droperidol, 3 inappropriate follow-up, 2 inability to use pain scale or PCA device, 1 PONV during post-op day 1

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Morphine consumption via PCA at Postoperative day 0; Group 1: mean 14.77 mg (SD 10); n=30, Group 2: mean 21.97 mg (SD 12); n=29
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain in nerve block group was lower; Group 1 Number missing: 6, Reason: 3 inappropriate follow-up, 1 sensitivity to adrenaline, 2 inability to use pain scale or PCA device; Group 2 Number missing: 7, Reason: 1 post-op treatment with droperidol, 3 inappropriate follow-up, 2 inability to use pain scale or PCA device, 1 PONV during post-op day 1

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

Protocol outcome 1: Postoperative pain at within 30 days
- Actual outcome: Pain at rest at Postoperative day 0; Group 1: mean 26.87 (SD 29); n=31, Group 2: mean 48.34 (SD 24); n=29; VAS 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain in nerve block group was lower; Group 1 Number missing: 4, Reason: 1 Bradycardia during surgery, 3 inappropriate follow-up; Group 2 Number missing: 7, Reason: 1 post-op treatment with droperidol, 3 inappropriate follow-up, 2 inability to use pain scale or PCA device, 1 PONV during post-op day 1

Protocol outcome 2: Postoperative use of analgesia at as reported
- Actual outcome: Morphine consumption via PCA at Postoperative day 0; Group 1: mean 2.32 mg (SD 4); n=31, Group 2: mean 21.97 mg (SD 12); n=29
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain in nerve block group was lower; Group 1 Number

missing: 4, Reason: 1 Bradycardia during surgery, 3 inappropriate follow-up; Group 2 Number missing: 7, Reason: 1 post-op treatment with droperidol, 3 inappropriate follow-up, 2 inability to use pain scale or PCA device, 1 PONV during post-op day 1	
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; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Tziona 2018[292]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Greece
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery until discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with ASA I-III who are scheduled for primary unilateral cemented TKA
Exclusion criteria	Contraindications to central and/or peripheral nerve blockade, previous major bone operation in the knee, bilateral or cementless TKA, allergy to any study medications, chronic opioid or gabapentin use, serious psychiatric, mental or cognitive disorder, language barrier or difficulty understanding or using PCA device.
Recruitment/selection of patients	September 2015 to March 2016.
Age, gender and ethnicity	Age - Mean (SD): 73 (7) and 72 (9). Gender (M:F): 9/31. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Regional - Regional anaesthesia with nerve block and local infiltration analgesia (during or after surgery). Ultrasound guided ACB using ropivacaine and dexamethasone. Spinal anaesthesia using ropivacaine. LIA using ropivacaine, adrenaline, and saline injected twice during surgery.. Duration Surgery until discharge. Concurrent medication/care: Premedication: pregabalin. Postoperative PCA using morphine. . Indirectness: No indirectness (n=20) Intervention 2: Regional - Regional anaesthesia with nerve block. Ultrasound guided ACB using ropivacaine and dexamethasone. Spinal anaesthesia using ropivacaine. Shame LIA using saline injected twice during surgery.. Duration Surgery until discharge. Concurrent medication/care: Premedication: pregabalin. Postoperative PCA using morphine. . Indirectness: No indirectness
Funding	Funding not stated (Authors stated no conflicts of interest)

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

Protocol outcome 1: Postoperative pain at within 30 days - Actual outcome: Pain while at rest at 6 hours after surgery; Group 1: mean 3 (SD 1.49); n=20, Group 2: mean 4.9 (SD 1.48); n=20; Numerical Rating Scale 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Postoperative use of analgesia at as reported - Actual outcome: Morphine consumption at 24 hours after surgery; Group 1: mean 16.75 mg (SD 9.51); n=20, Group 2: mean 28.45 mg (SD 14.09); n=20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Nausea at within 30 days - Actual outcome: Nausea at Within 24 hours of surgery; Group 1: 1/20, Group 2: 2/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at within 90 days; Quality of life at within 30 days; Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days; Length of stay at .; Mobilisation within 24 hours after surgery at .

Study	Uesugi 2014[293]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in Japan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 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	People with osteoarthritis of the knee who were scheduled to undergo TKA.
Exclusion criteria	Scheduled to undergo simultaneous bilateral TKA and those with a previous history of knee joint surgery,rheumatoid arthritis, regular narcotic use, psychiatric disorder, neuromuscular disorder,severe systemic disorder (heart failure, respiratory organ failure, kidney failure, liver failure, or clotting disorder), drug allergy to study medications.
Recruitment/selection of patients	August to December in 2012.
Age, gender and ethnicity	Age - Mean (SD): 76 (6) and 76 (7). Gender (M:F): 41/159. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: ASA grade I or II (I-II).
Indirectness of population	No indirectness
Interventions	(n=105) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacaine. LIA using ropivacaine, adrenaline, morphine hydrochloride, dexamethasone and saline. This was injected at 2 points during surgery.. Duration Surgery until discharge. Concurrent medication/care: If people complained of postoperative pain they were given diclofenac sodium suppositories.. Indirectness: No indirectness (n=105) Intervention 2: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia using bupivacaine. Femoral and sciatic nerve block using ropivacaine.. Duration Surgery until discharge. Concurrent medication/care: If people complained of postoperative pain they were given diclofenac sodium suppositories.. Indirectness: No indirectness
Funding	No funding ("This research did not receive any external funding")

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 pain at within 30 days - Actual outcome: Time until onset of pain at .; Group 1: mean 8.4 hours (SD 9.2); n=100, Group 2: mean 15.3 hours (SD 8.4); n=100 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: 5, Reason: Excluded from analysis due to postoperative delirium ; Group 2 Number missing: 5, Reason: Excluded from analysis due to postoperative delirium Protocol outcome 2: Postoperative use of analgesia at as reported - Actual outcome: Number of suppositories used at 48 hours after surgery; Group 1: mean 2.9 (SD 1.4); n=100, Group 2: mean 2.8 (SD 1.3); n=100 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: 5, Reason: Excluded from analysis due to postoperative delirium ; Group 2 Number missing: 5, Reason: Excluded from analysis due to postoperative delirium Protocol outcome 3: Nausea at within 30 days - Actual outcome: Nausea and vomiting at Postoperative period; Group 1: 12/100, Group 2: 8/100 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: 5, Reason: Excluded from analysis due to postoperative delirium ; Group 2 Number missing: 5, Reason: Excluded from analysis due to postoperative delirium	
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; Length of stay at .; Mobilisation within 24 hours after surgery at .

Study	Vaishya 2015[294]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in India; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and follow-up for 4-7 days.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People scheduled for unilateral primary TKA with American society of anaesthesiologists (ASA) physical status I to III
Exclusion criteria	People with history of allergy to any of the study drugs, drug abuse, uncontrolled hypertension, history of stroke or a major neurological deficit, uncontrolled angina or chronic medical illness
Recruitment/selection of patients	May - December 2012.
Age, gender and ethnicity	Age - Mean (SD): 64 (10) and 65 (9). Gender (M:F): 21/59. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (I-III).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacaine heavy with preservative free fentanyl. LIA using bupivacaine, morphine, ketorolac, adrenaline, gentamycin, and saline. It was injected at 3 points during surgery.. Duration Surgery until discharge. Concurrent medication/care: Postoperative pain relief: patient controlled analgesia (PCA) using morphine, IV Amoxicillin-clavulanate, IV paracetamol, IV diclofenac, subcut enoxparin.. Indirectness: No indirectness (n=40) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthesia using bupivacaine heavy with preservative free fentanyl. LIA placebo using saline. It was injected at 3 points during surgery.. Duration Surgery until discharge. Concurrent medication/care: Postoperative pain relief: patient controlled analgesia (PCA) using morphine, IV Amoxicillin-clavulanate, IV paracetamol, IV diclofenac, subcut enoxparin.. Indirectness: No indirectness
Funding	No funding ("No benefits or funds were received in support of this study")

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: Pain during exercise at 1st postoperative day; Group 1: mean 3.5 (SD 1.89); n=40, Group 2: mean 4.32 (SD 1.89); n=40; VAS 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, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: ASA not detailed; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 4.5 days (SD 0.67); n=40, Group 2: mean 5.7 days (SD 0.64); n=40 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 not detailed; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Nausea at within 30 days - Actual outcome: Nausea at Postoperative period in hospital; Group 1: 3/40, Group 2: 5/40 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 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 neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days; Postoperative use of analgesia at as reported; Mobilisation within 24 hours after surgery at .

Study	Wallace 2012[300]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=46)
Countries and setting	Conducted in United Kingdom; Setting: Single university hospital.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 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 undergoing primary unilateral TKR
Exclusion criteria	People who lacked capacity to give consent, contraindication to study analgesics, renal failure.
Age, gender and ethnicity	Age - Median (IQR): 63.5 (61-74) and 63.5 (55.5 to 65). Gender (M:F): 23/23. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: General - General anaesthesia with local infiltration analgesia (during or after procedure). General anaesthesia. Peri-articular infiltration using levobupivacaine, morphine, ketorolac, adrenaline, and saline. Half before implantation and half before closure. . Duration Surgery and in-hospital period. Concurrent medication/care: Auto-transfusion drain used. . Indirectness: No indirectness (n=23) Intervention 2: General - General anaesthesia with nerve block. General anaesthesia. Femoral nerve block using levobupivacaine. . Duration Surgery and in-hospital period. Concurrent medication/care: Auto-transfusion drain used. . Indirectness: No indirectness
Funding	Study funded by industry (Funded by grant from Astra Tech Ltd.)
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; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Watson 2005[305]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=32)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery until discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with osteoarthritis scheduled for primary unilateral bicompartmental cemented TKA.
Exclusion criteria	Morbid obesity, contraindication to regional anaesthesia, ASA IV or V, peripheral neuropathy, chronic opioid use, allergy to local anaesthetic or morphine.
Age, gender and ethnicity	Age - Mean (SD): 69 (7) and 72 (7). Gender (M:F): 17/15. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Mixed (ASA I-III).
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Regional - Regional anaesthesia with nerve block and local infiltration analgesia (during or after surgery). Spinal anaesthesia using bupivacaine. Lumbar plexus block using levobupivacaine. Sciatic nerve block using levobupivacaine. LIA using levobupivacaine infused into the plexus block catheter postoperatively. . Duration Surgery and 48 subsequent hours . Concurrent medication/care: Premedication: temazepam. Sedation using fentanyl and midazolam. Postoperative oral analgesics given and PCA using morphine. . Indirectness: No indirectness (n=16) Intervention 2: Regional - Regional anaesthesia with nerve block. Spinal anaesthesia using bupivacaine. Lumbar plexus block using levobupivacaine. Sciatic nerve block using levobupivacaine. LIA placebo using saline infused into the plexus block catheter postoperatively. . Duration Surgery and 48 subsequent hours . Concurrent medication/care: Premedication: temazepam. Sedation using fentanyl and midazolam. Postoperative oral analgesics given and PCA using morphine. . Indirectness: No indirectness
Funding	Academic or government funding (Likely to have been NHS funded)

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

Protocol outcome 1: Mobilisation within 24 hours after surgery at . - Actual outcome: Mobilisation at first postoperative day; Group 1: 5/16, Group 2: 0/16 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; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days

Study	Widmer 2012[307]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=55)
Countries and setting	Conducted in Australia
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 1 year 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 86 years old scheduled for unilateral primary TKA
Exclusion criteria	Allergy to a study medication, anatomical aberrations in the inguinal area, history of drug or alcohol abuse, significant cognitive impairment, postoperative endotracheal intubation, postoperative use of greater than 40mg oral morphine, severe cardiac, hepatic or renal disease.
Recruitment/selection of patients	People presenting to either of two senior authors.
Age, gender and ethnicity	Age - Median (IQR): 72 (64-77) and 69 (63-76). Gender (M:F): 30/24. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: General - General anaesthesia with nerve block and local infiltration analgesia (during or after procedure). General using propofol. Sevoflurane used for maintenance. Preoperative femoral nerve block using ropivacaine. LIA during the surgery using ropivacaine and adrenaline. . Duration Surgery and in hospital period. Concurrent medication/care: Premedication using IV midazolam. Postoperative PCA given to all people programmed to deliver fentanyl. . Indirectness: No indirectness (n=28) Intervention 2: General - General anaesthesia with local infiltration analgesia (during or after procedure). General using propofol. Sevoflurane used for maintenance. Sham preoperative femoral nerve block used. LIA during the surgery using ropivacaine and adrenaline. . Duration Surgery and in hospital period. Concurrent medication/care: Premedication using IV midazolam. Postoperative PCA given to all people programmed to deliver fentanyl. . Indirectness: No indirectness
Funding	Funding not stated (No conflicts of interest was stated)

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

INFILTRATION ANALGESIA (DURING OR AFTER PROCEDURE) versus GENERAL ANAESTHESIA WITH LOCAL INFILTRATION ANALGESIA (DURING OR AFTER PROCEDURE) Protocol outcome 1: Postoperative pain at within 30 days - Actual outcome: Pain at 24 hours after surgery; Group 1: mean 2.4 (SD 0.9); n=27, Group 2: mean 2.5 (SD 0.9); n=28; Unclear 0-4 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, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in WOMAC score and KSS knee score and SD-36 physical scale. ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Thromboembolic complications at within 90 days - Actual outcome: Thromboembolic events at In-hospital period; Group 1: 0/27, Group 2: 0/28 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: Some difference in WOMAC score and KSS knee score and SD-36 physical scale. ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Postoperative use of analgesia at as reported - Actual outcome: PCA fentanyl use at Within 24 hours of surgery; Group 1: mean 0.973 mg (SD 0.4267); n=27, Group 2: mean 1.502 mg (SD 0.7063); n=28 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: Some difference in WOMAC score and KSS knee score and SD-36 physical scale. ; 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; Hospital readmissions at within 30 days; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

Study	Williams 2013[311]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=67)
Countries and setting	Conducted in Canada
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 1 year follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults 18-90 years old with osteoarthritis who are scheduled to undergo primary unilateral TKA
Exclusion criteria	Inflammatory arthritis, significant pain of other origin, chronic pain or neuromuscular disorder, allergy to any study medications, contraindications to spinal anaesthesia, inability to tolerate narcotics, liver or kidney dysfunction.
Age, gender and ethnicity	Age - Mean (SD): 66 (10) and 67 (13). Gender (M:F): 21/30. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Mixed (ASA I-IV).
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Regional - Regional anaesthesia with local infiltration analgesia (during or after surgery). Spinal anaesthetic using bupivacaine and fentanyl. Continuous LIA via a catheter using bupivacaine for 48 hours after the surgery. . Duration Surgery until discharge. Concurrent medication/care: People sedated with midazolam and propofol. Two standard intraoperative loading dose of bupivacaine and epinephrine. Postoperative PCA using morphine. . Indirectness: No indirectness (n=25) Intervention 2: Regional - Regional anaesthesia. Spinal anaesthetic using bupivacaine and fentanyl. Continuous LIA placebo via a catheter using saline for 48 hours after the surgery. . Duration Surgery until discharge. Concurrent medication/care: People sedated with midazolam and propofol. Two standard intraoperative loading dose of bupivacaine and epinephrine. Postoperative PCA using morphine. . 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: Postoperative pain at within 30 days - Actual outcome: Pain at 6-8 hours after surgery; Group 1: mean 2.4 (SD 2.3); n=24, Group 2: mean 3.1 (SD 2.9); n=25; VAS 0-10 Top=High is poor outcome 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: More ASA 4 people in treatment group; Group 1 Number missing: 2, Reason: One person could not tolerate analgesic medication, another was removed to the cardia unit; Group 2 Number missing: Protocol outcome 2: Postoperative use of analgesia at as reported - Actual outcome: Morphine consumption via PCA at 48 hours after surgery; Group 1: mean 39 mg (SD 27.1); n=24, Group 2: mean 53 mg (SD 30.4); n=25 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: More ASA 4 people in treatment group; Group 1 Number missing: 2, Reason: One person could not tolerate analgesic medication, another was removed to the cardia unit; Group 2 Number missing: Protocol outcome 3: Length of stay at . - Actual outcome: Hospital length of stay at .; Group 1: mean 4.7 days (SD 2.3); n=24, Group 2: mean 3.9 days (SD 1.1); n=25 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: More ASA 4 people in treatment group; Group 1 Number missing: 2, Reason: One person could not tolerate analgesic medication, another was removed to the cardia unit; Group 2 Number missing: Protocol outcome 4: Nausea at within 30 days - Actual outcome: Nausea/vomit at Within 24 hours of surgery; Group 1: 1/24, Group 2: 3/25 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: More ASA 4 people in treatment group; Group 1 Number missing: 2, Reason: One person could not tolerate analgesic medication, another was removed to the cardia unit; 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; Mobilisation within 24 hours after surgery at .

Study (subsidiary papers)	Williams-russo 1995[310] (Williams-russo 1996[309])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=262)
Countries and setting	Conducted in USA; Setting: Hospital for Special Surgery, New York.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 months 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 elective unilateral TKA. People had to be over 40 years of age, able to speak English, absence of serious hearing or visual impairment.
Exclusion criteria	Surgery performed with regional or general anaesthetic within past 3 months, contraindications to epidural anaesthesia, history of extensive Harrington rod spinal fusion, cancer metastatic to lumbar or thoracic vertebrae, history of bleeding diathesis, local infection at the site of epidural anaesthesia, contraindications to general anaesthesia.
Recruitment/selection of patients	1989-1992
Age, gender and ethnicity	Age - Median (range): 69. Gender (M:F): 121/141. Ethnicity: Not detailed
Further population details	1. Age: Mixed 2. ASA grade: Not stated / Unclear
Indirectness of population	Serious indirectness: Treatments contain varying postoperative analgesia.
Interventions	(n=134) Intervention 1: Regional - Regional anaesthesia. Epidural anaesthesia using lidocaine or bupivacaine. . Duration Surgery and in-hospital period. Concurrent medication/care: Preoperative sedation not utilised. 95% of people received postoperative epidural anaesthesia for 12 to 72 hours. . Indirectness: No indirectness (n=128) Intervention 2: General - General anaesthesia. Induction using thiopental sodium, fentanyl and vecuronium. Maintenance with fentanyl and nitrous oxide. . Duration Surgery and in-hospital period. Concurrent medication/care: Preoperative sedation not utilised. All people received postoperative IV analgesia.. Indirectness: No indirectness
Funding	Academic or government funding (Supported by a grant from National Institute of Aging and in part by the Cornell Arthritis and Disease Musculoskeletal Diseases Center.)

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 2 months after surgery; Group 1: 1/133, Group 2: 1/120
Risk of bias: All domain - Very 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: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms. ; Group 2 Number missing: 8, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms.

Protocol outcome 2: Postoperative neurocognitive decline at within 30 days
- Actual outcome: Linguistic domain: Boston Naming test at 1 week after surgery; Group 1: mean -0.3 (SD 2.6); n=133, Group 2: mean 0 (SD 2.5); n=120; Boston Naming 0-30 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms. ; Group 2 Number missing: 8, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms.
- Actual outcome: Psychomotor/Attention domain: digit symbol at 1 week after surgery; Group 1: mean -3.7 (SD 6.1); n=133, Group 2: mean -2.7 (SD 6); n=120
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: 1, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms. ; Group 2 Number missing: 8, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms.
- Actual outcome: Memory domain: Benton Visual Retention at 1 week after surgery; Group 1: mean -0.8 (SD 2); n=133, Group 2: mean -0.8 (SD 1.9); n=120; Benton Visual Retention 0-10 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms. ; Group 2 Number missing: 8, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms.
- Actual outcome: Delirium at Unclear; Group 1: 16/133, Group 2: 12/120
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: 1, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms. ; Group 2 Number missing: 8, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms.

Protocol outcome 3: Thromboembolic complications at within 90 days
- Actual outcome: DVT at Unclear; Group 1: 39/97, Group 2: 39/81
Risk of bias: All domain - Very 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: 3 postoperative complications and

transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms. ; Group 2 Number missing: 8, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms. Protocol outcome 4: Length of stay at . - Actual outcome: Length of stay at .; Group 1: mean 12.1 days (SD 4.5); n=133, Group 2: mean 12.7 days (SD 4.3); n=120 Risk of bias: All domain - Very 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: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms. ; Group 2 Number missing: 8, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms. Protocol outcome 5: Mobilisation within 24 hours after surgery at . - Actual outcome: Time until able to transfer unassisted at .; Group 1: mean 6.6 days (SD 2.9); n=133, Group 2: mean 6.9 days (SD 3.4); n=120 Risk of bias: All domain - Very 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: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms. ; Group 2 Number missing: 8, Reason: 3 postoperative complications and transferred to intensive care unit, 2 combined general and regional, 4 did not have complete forms.	
Protocol outcomes not reported by the study	Quality of life at within 30 days; Postoperative pain at within 30 days; Hospital readmissions at within 30 days; Postoperative use of analgesia at as reported; Nausea at within 30 days

Study	Yadeau 2005[317]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with follow-up until discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People under 85 years old with osteoarthritis scheduled for primary TKA
Exclusion criteria	previous knee trauma, previous surgery to operative knee, peripheral neuropathy, chronic preoperative opioid usage, non palpable femoral artery, previous lower extremity vascular bypass surgery.
Age, gender and ethnicity	Age - Mean (SD): 72 (8) and 73 (8). Gender (M:F): Not detailed. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Regional - Regional anaesthesia with nerve block. Combine spinal epidural anaesthesia using bupivacaine. Femoral nerve block using bupivacaine and epinephrine. . Duration Surgery until discharge. Concurrent medication/care: Postoperative patient controlled epidural anaesthesia using bupivacaine and hydromorphone. Oral analgesics (acetaminophen, hydrocodone, oxycodone) offered when PCEA removed. . Indirectness: No indirectness (n=39) Intervention 2: Regional - Regional anaesthesia. Combine spinal epidural anaesthesia using bupivacaine. Femoral nerve block placebo using saline. Duration Surgery until discharge. Concurrent medication/care: Postoperative patient controlled epidural anaesthesia using bupivacaine and hydromorphone. Oral analgesics (acetaminophen, hydrocodone, oxycodone) offered when PCEA removed.. Indirectness: No indirectness
Funding	Academic or government funding
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: VAS pain >/=6 at On postoperative day 1; Group 1: 2/41, Group 2: 12/39 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Nausea at within 30 days - Actual outcome: Nausea at Within 3 days of surgery; Group 1: 11/41, Group 2: 11/39 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at within 90 days; Quality of life at within 30 days; Postoperative neurocognitive decline at within 30 days; Thromboembolic complications at within 90 days; Hospital readmissions at within 30 days; Postoperative use of analgesia at as reported; Length of stay at .; Mobilisation within 24 hours after surgery at .

Study	Youm 2016[320]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in South Korea; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People 80 years old or younger with osteoarthritis who are scheduled to have unilateral TKA.
Exclusion criteria	Bilateral or revision arthroplasty, neurologic disorder, coagulopathy, hypersensitive to local anaesthetics, unable to understand pain scales or use PCA.
Recruitment/selection of patients	March 2014 to March 2015.
Age, gender and ethnicity	Age - Mean (SD): 68, 70, 68. Gender (M:F): 11/79. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear 2. ASA grade: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: General - General anaesthesia with nerve block and local infiltration analgesia (during or after procedure). General anaesthesia. Femoral nerve block using ropivacaine. LIA using ropivacaine, morphine, epinephrine, methylprednisoline, ketorolac, cefoxitin, and saline. Injected before fixation of the implants. . Duration Surgery until discharge. Concurrent medication/care: Premedication: celecoxib, acetaminophen, tramadol, and pregabalin. Postoperative pain control via IV PCA using fentanyl and nefopam. People also given celecoxib, acetaminophen, tramadol, and pregabalin. IV morphine used for severe pain. . Indirectness: No indirectness (n=30) Intervention 2: General - General anaesthesia with local infiltration analgesia (during or after procedure). General anaesthesia. LIA using ropivacaine, morphine, epinephrine, methylprednisoline, ketorolac, cefoxitin, and saline. Injected before fixation of the implants. . Duration Surgery until discharge. Concurrent medication/care: Premedication: celecoxib, acetaminophen, tramadol, and pregabalin. Postoperative pain control via IV PCA using fentanyl and nefopam. People also given celecoxib, acetaminophen, tramadol, and pregabalin. IV morphine used for severe pain. . Indirectness: No indirectness (n=30) Intervention 3: General - General anaesthesia with nerve block. General anaesthesia. Femoral nerve

	block using ropivacaine. . Duration Surgery until discharge. Concurrent medication/care: Premedication: celecoxib, acetaminophen, tramadol, and pregabalin. Postoperative pain control via IV PCA using fentanyl and nefopam. People also given celecoxib, acetaminophen, tramadol, and pregabalin. IV morphine used for severe pain. . Indirectness: No indirectness
Funding	Funding not stated (It was stated that the authors have 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; Postoperative use of analgesia at as reported; Length of stay at .; Nausea at within 30 days; Mobilisation within 24 hours after surgery at .

1 Appendix E: Forest plots

E.1 2 Regional anaesthesia versus general anaesthesia

Figure 2: Mortality up to 90 days

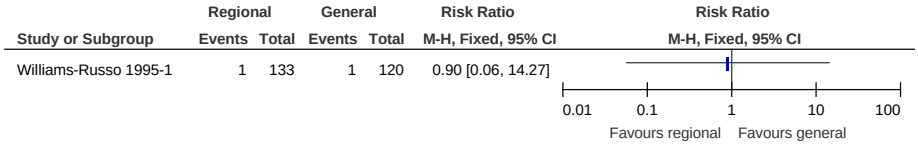


Figure 3: Postoperative neurocognitive decline up to 30 days

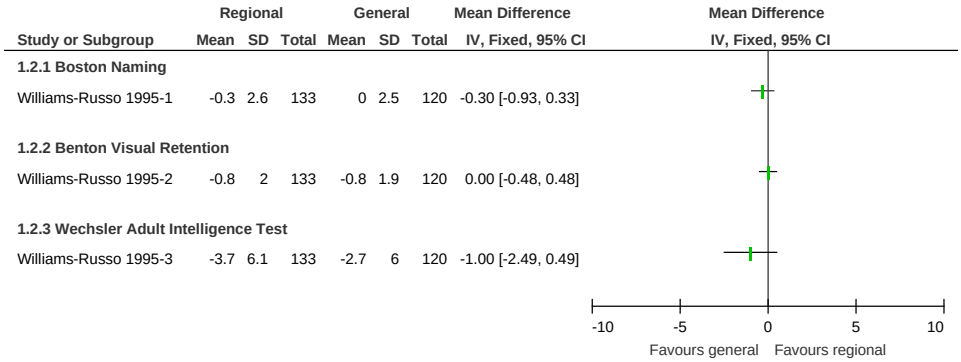


Figure 4: Postoperative neurocognitive decline via delirium in hospital

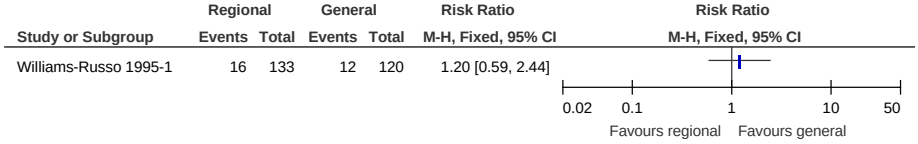


Figure 5: Thromboembolic complications up to 90 days

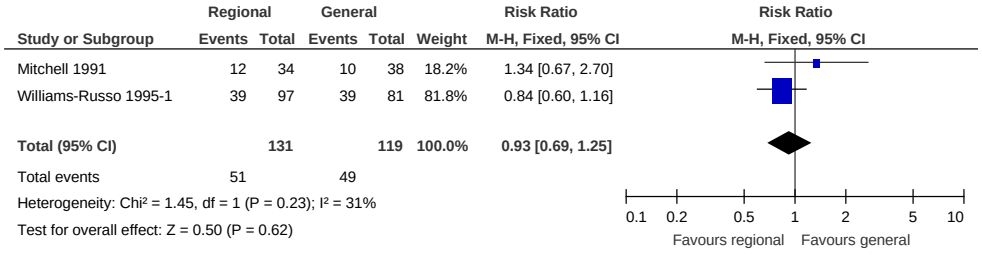


Figure 6: Length of stay

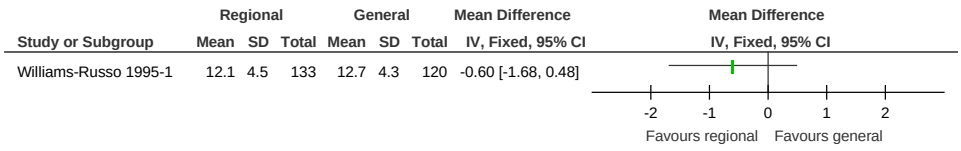
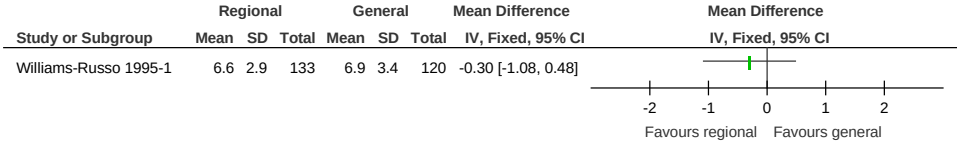


Figure 7: Mobilisation: time until transfer unassisted



E.2 Regional anaesthesia versus general anaesthesia with nerve block

Figure 8: Postoperative pain up to 30 days

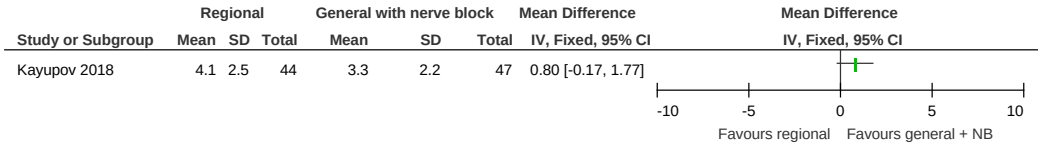


Figure 9: Length of stay

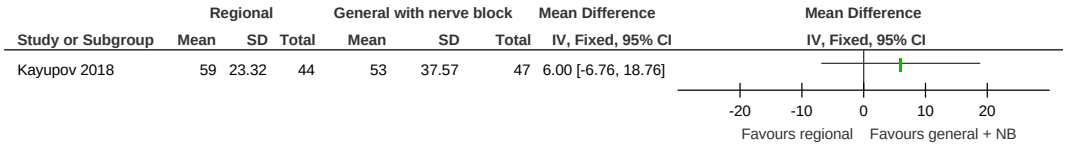
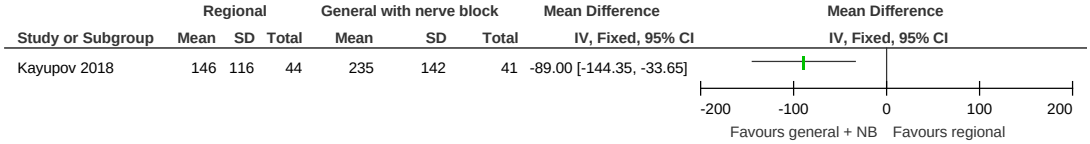


Figure 10: Mobilisation: ambulating distance on postoperative day 1



E.3 Regional anaesthesia with LIA versus general anaesthesia with LIA

Figure 11: Thromboembolic complications up to 90 days

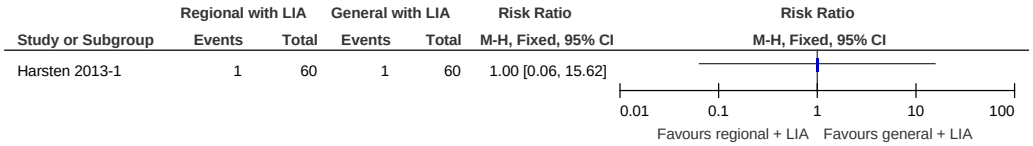


Figure 12: Length of stay

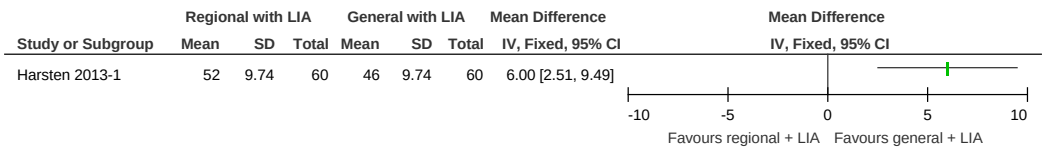


Figure 13: Nausea up to 30 days

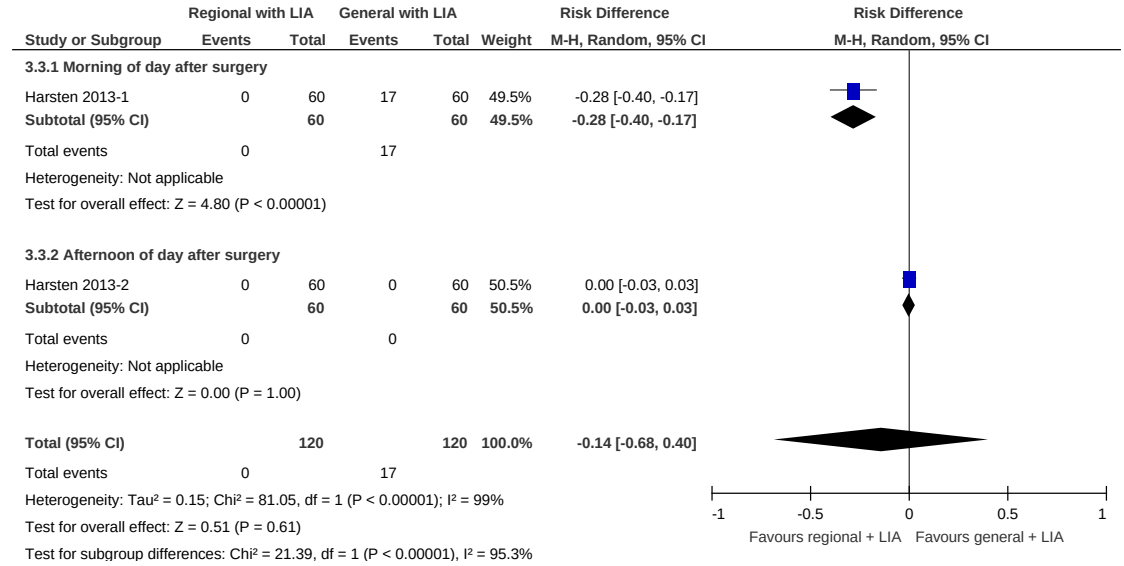
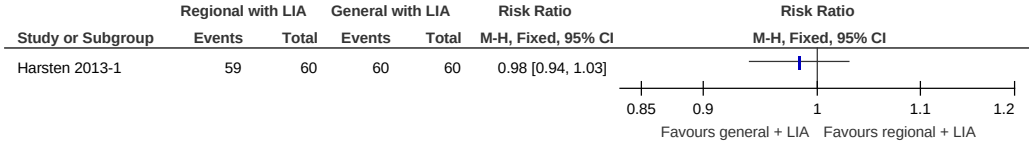


Figure 14: Mobilisation within 24 hours after surgery



E.4 Regional anaesthesia with nerve block versus general anaesthesia with nerve block

Figure 15: Postoperative pain up to 30 days

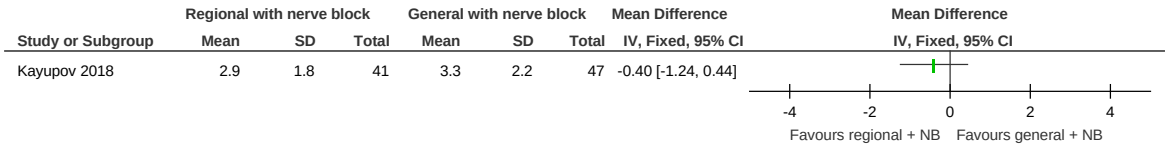


Figure 16: Length of stay

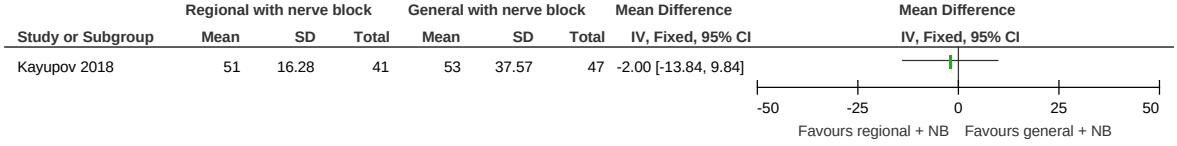
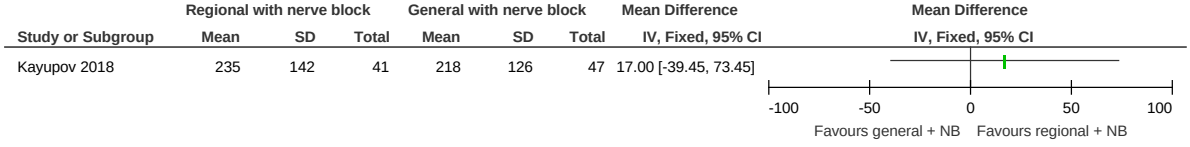


Figure 17: Mobilisation: ambulation distance on postoperative day 1



E.5 General and regional anaesthesia versus general anaesthesia and nerve block

Figure 18: Postoperative pain: no pain on movement

Study or Subgroup	General and regional Events	Total	General with nerve block Events	Total	Risk Ratio M-H, Fixed, 95% CI
Davies 2004	23	29	16	30	1.49 [1.01, 2.18]

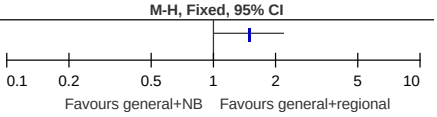


Figure 19: Nausea up to 30 days

Study or Subgroup	General and regional Events	Total	General with nerve block Events	Total	Risk Ratio M-H, Fixed, 95% CI
Sakai 2013	6	30	4	30	1.50 [0.47, 4.78]

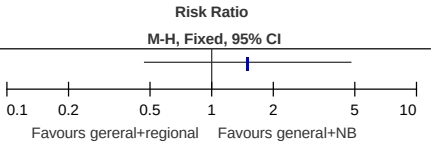
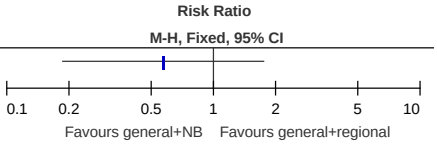


Figure 20: Mobilisation within 24 hours after surgery

Study or Subgroup	General and regional Events	Total	General with nerve block Events	Total	Risk Ratio M-H, Fixed, 95% CI
Sakai 2013	4	30	7	30	0.57 [0.19, 1.75]



E.6 Regional anaesthesia with LIA versus regional anaesthesia

Figure 21: Postoperative pain up to 30 days

Study or Subgroup	Regional with LIA Mean	SD	Total	Regional Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Dimaculangan 2019	3.76	3.53	23	3.52	2.79	21	6.2%	0.24 [-1.63, 2.11]
Goyal 2013-1	3.03	2.311	75	3.959	2.311	75	39.7%	-0.93 [-1.67, -0.19]
Han 2007-1	1.7	2.7	30	1.8	3.1	15	6.4%	-0.10 [-1.94, 1.74]
Han 2007-2	2.3	3.1	30	1.8	3.1	15	5.9%	0.50 [-1.42, 2.42]
Vaishya 2015	3.5	1.89	40	4.32	1.89	40	31.7%	-0.82 [-1.65, 0.01]
Williams 2013	2.4	2.3	24	3.1	2.9	25	10.2%	-0.70 [-2.16, 0.76]
Total (95% CI)			**222**			**191**	**100.0%**	**-0.66 [-1.13, -0.20]**

Heterogeneity: Chi² = 3.30, df = 5 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)

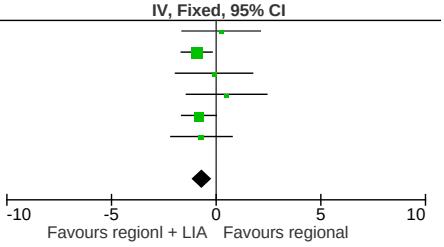


Figure 22: Postoperative pain: removed from study due to severe pain

Study or Subgroup	Regional with LIA Events	Total	Regional Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Niemelainen 2014	0	27	3	29	0.13 [0.01, 1.35]

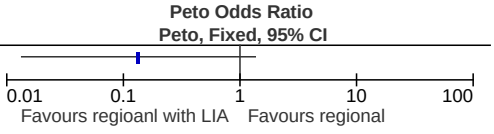


Figure 23: Thromboembolic complications up to 90 days

Study or Subgroup	Regional with LIA Events	Total	Regional Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Goyal 2013-1	1	75	0	75	50.0%	7.39 [0.15, 372.38]
Hinarejos 2016	0	50	1	50	50.0%	0.14 [0.00, 6.82]
Total (95% CI)		**125**		**125**	**100.0%**	**1.00 [0.06, 15.99]**
Total events	1		1			

Heterogeneity: Chi² = 2.00, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 0.00 (P = 1.00)

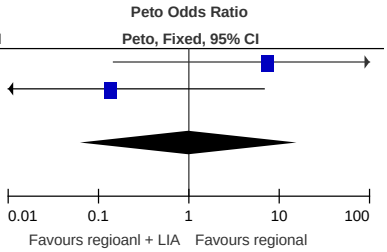


Figure 24: Hospital readmission up to 30 days

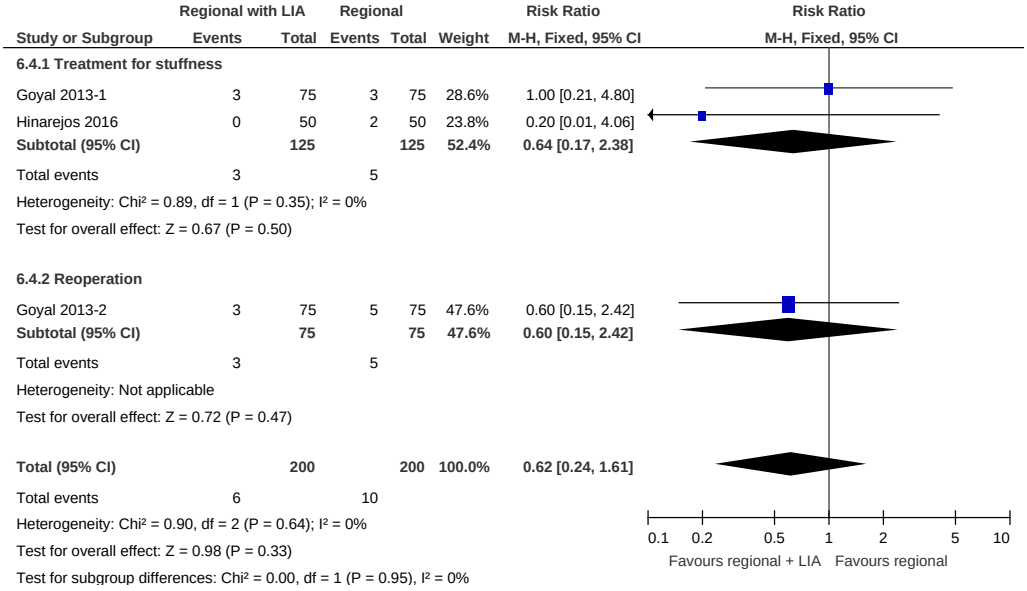


Figure 25: Postoperative use of analgesia: use of rescue medication

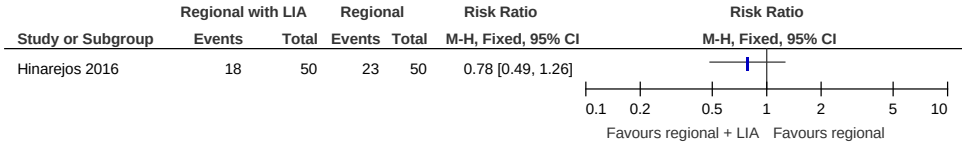


Figure 26: Postoperative use of analgesia

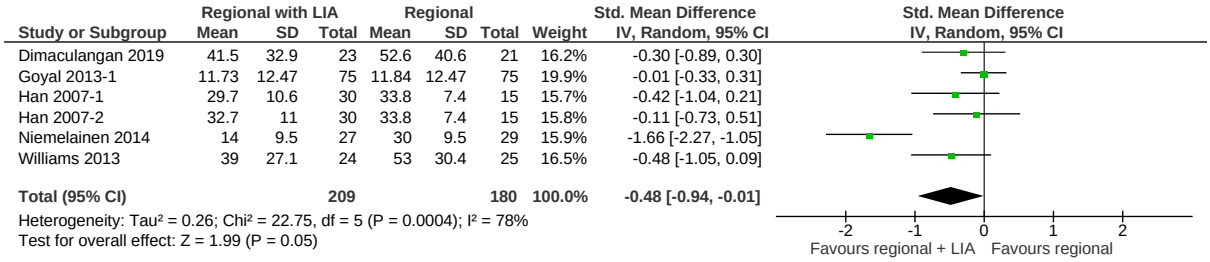


Figure 27: Length of stay

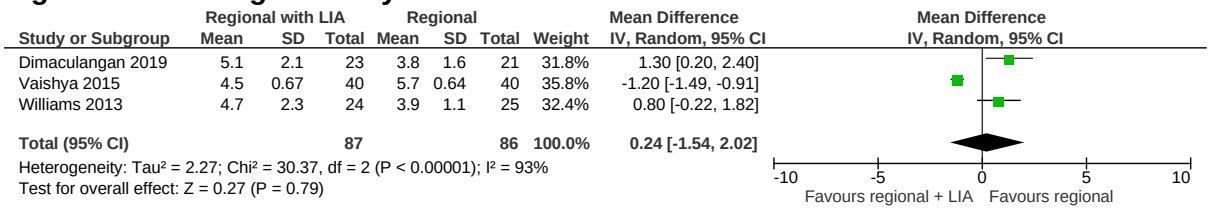
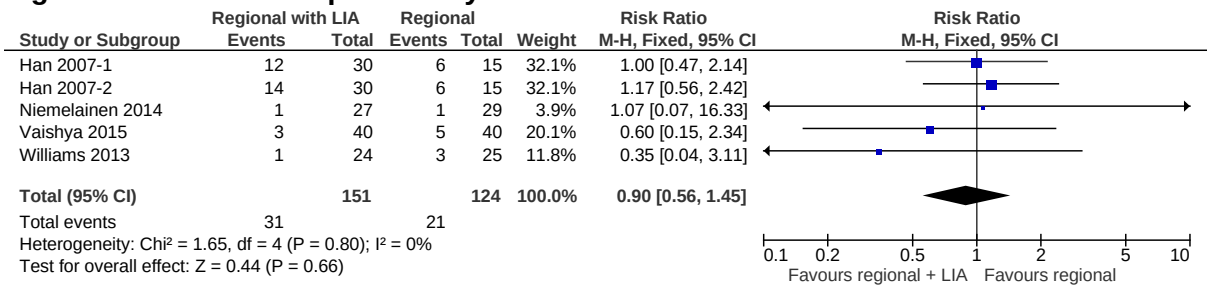


Figure 28: Nausea up to 30 days



E.7 Regional anaesthesia with nerve block versus regional anaesthesia

Figure 29: Postoperative pain on day 1 (VAS >/= 6)

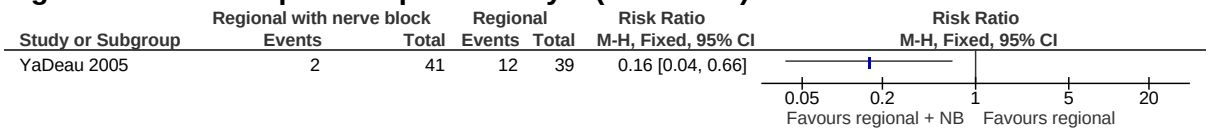


Figure 30: Postoperative pain up to 30 days

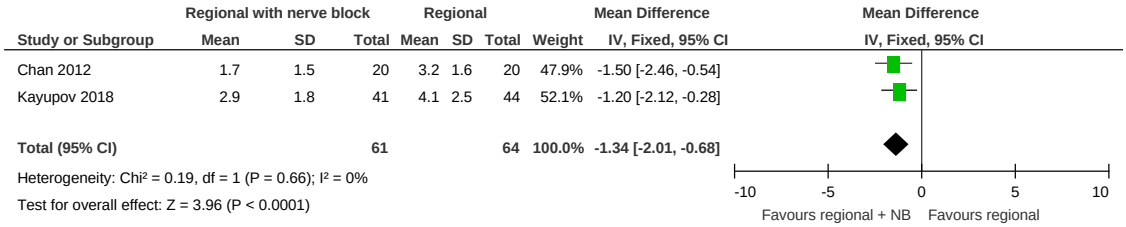


Figure 31: Postoperative use of analgesia

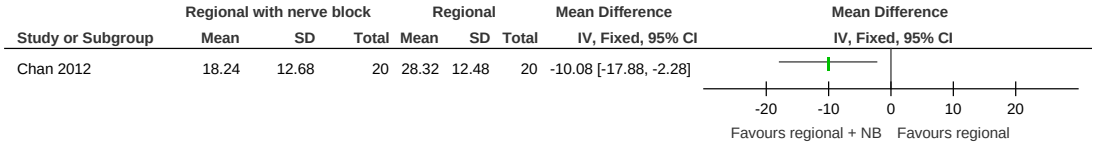


Figure 32: Length of stay

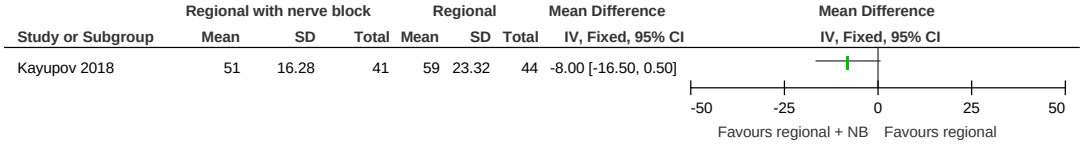


Figure 33: Nausea up to 30 days

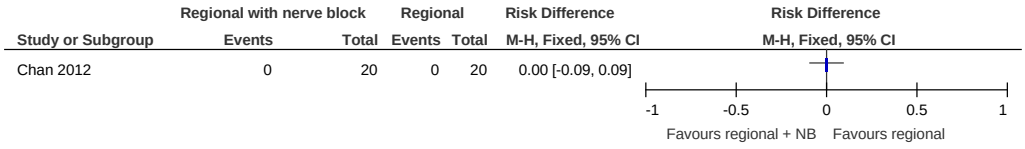
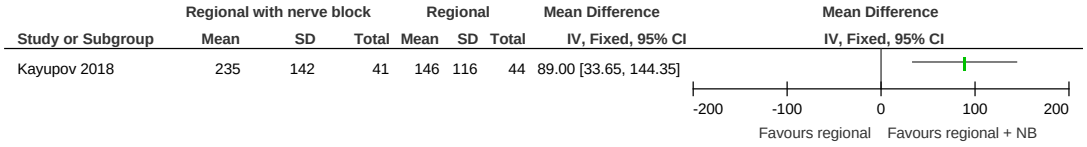


Figure 34: Mobilisation: ambulation distance on Postoperative day 1



E.8 Regional anaesthesia with LIA versus regional anaesthesia with nerve block

Figure 35: Postoperative pain up to 30 days

Study or Subgroup	Regional with LIA Mean	SD	Total	Regional with nerve block Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ashraf 2013	1.6	2.4	19	3.6	3.2	21	10.2%	-2.00 [-3.74, -0.26]
Choi 2016	2.5	2.3	41	3.9	2.2	39	31.9%	-1.40 [-2.39, -0.41]
Grosso 2018	3.8	2.4	51	3.9	2.3	53	38.0%	-0.10 [-1.00, 0.80]
Sawhney 2016	4.9	3.1	49	6.2	3.1	46	19.9%	-1.30 [-2.55, -0.05]
Total (95% CI)			**160**			**159**	**100.0%**	**-0.95 [-1.50, -0.39]**

Heterogeneity: Chi² = 5.89, df = 3 (P = 0.12); I² = 49%
Test for overall effect: Z = 3.34 (P = 0.0009)

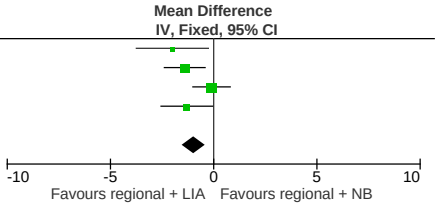


Figure 36: Postoperative pain: time to onset

Study or Subgroup	Regional with LIA Mean	SD	Total	Regional with nerve block Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Uesugi 2014	8.4	9.2	100	15.3	8.4	100	-6.90 [-9.34, -4.46]

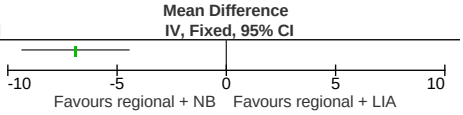


Figure 37: Thromboembolic complications up to 90 days

Study or Subgroup	Regional with LIA Events	Total	Regional with nerve block Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Sogbein 2017	0	35	1	35	0.14 [0.00, 6.82]

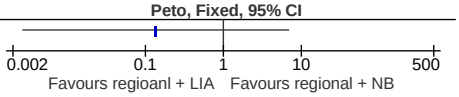


Figure 38: Hospital readmission up to 30 days

Study or Subgroup	Regional with LIA Events	Total	Regional with nerve block Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Moghtadaei 2014	1	20	0	20	7.39 [0.15, 372.38]

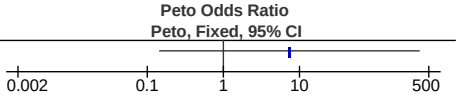


Figure 39: Postoperative use of analgesia in mg

Study or Subgroup	Regional with LIA Mean	SD	Total	Regional with nerve block Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Uesugi 2014	2.9	1.4	100	2.8	1.3	100	0.10 [-0.27, 0.47]

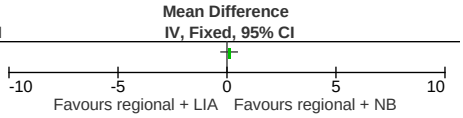


Figure 40: Postoperative use of analgesia in mg

Study or Subgroup	Regional with LIA Mean	SD	Total	Regional with nerve block Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ashraf 2013	115	50.3	19	176.5	103.2	21	14.3%	-0.73 [-1.37, -0.09]
Choi 2016	77.2	40.8	41	93.7	45.2	39	20.8%	-0.38 [-0.82, 0.06]
Grosso 2018	100	62	51	131	74	53	22.9%	-0.45 [-0.84, -0.06]
Sawhney 2016	5	6.9	49	7	5.6	46	22.3%	-0.31 [-0.72, 0.09]
Sogbein 2017	8.88	1.79	35	8.27	1.73	35	19.7%	0.34 [-0.13, 0.81]
Total (95% CI)			**195**			**194**	**100.0%**	**-0.29 [-0.61, 0.03]**

Heterogeneity: Tau² = 0.07; Chi² = 9.52, df = 4 (P = 0.05); I² = 58%
Test for overall effect: Z = 1.79 (P = 0.07)

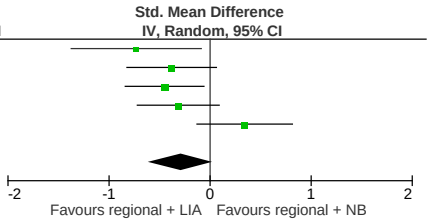


Figure 41: Length of stay

Study or Subgroup	Regional with LIA Mean	SD	Total	Regional with nerve block Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ashraf 2013	5.4	1.2	19	5.7	1.3	21	16.8%	-0.30 [-1.07, 0.47]
Grosso 2018	2.5	1.2	51	2.9	1.5	53	37.2%	-0.40 [-0.92, 0.12]
Sogbein 2017	2.2	1	35	2.4	1	35	46.0%	-0.20 [-0.67, 0.27]
Total (95% CI)			**105**			**109**	**100.0%**	**-0.29 [-0.61, 0.03]**

Heterogeneity: Chi² = 0.31, df = 2 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.80 (P = 0.07)

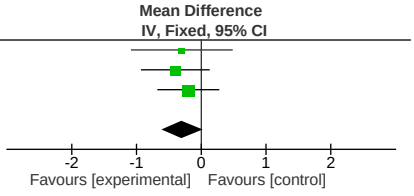


Figure 42: Mobilisation within 24 hours after surgery

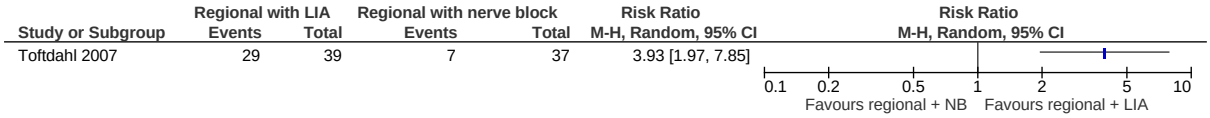
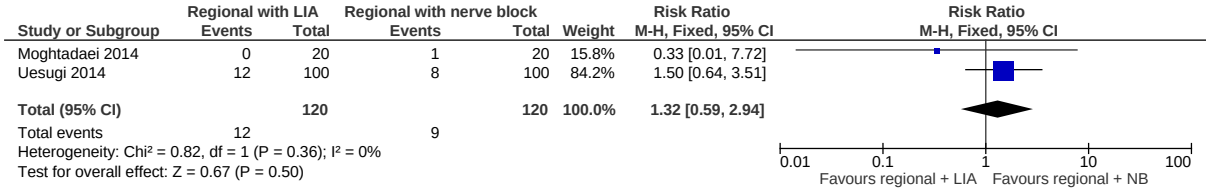


Figure 43: Nausea



E.91 Regional anaesthesia with nerve block and LIA versus
2 regional anaesthesia with LIA

Figure 44: Postoperative pain requiring rescue IV PCA

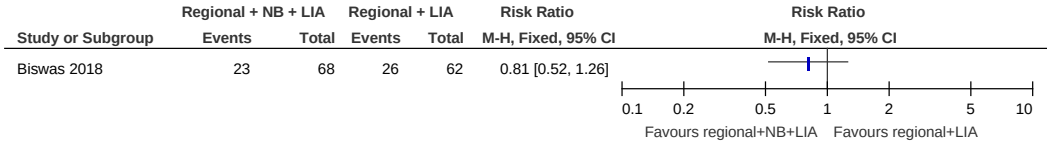


Figure 45: Postoperative pain up to 30 days

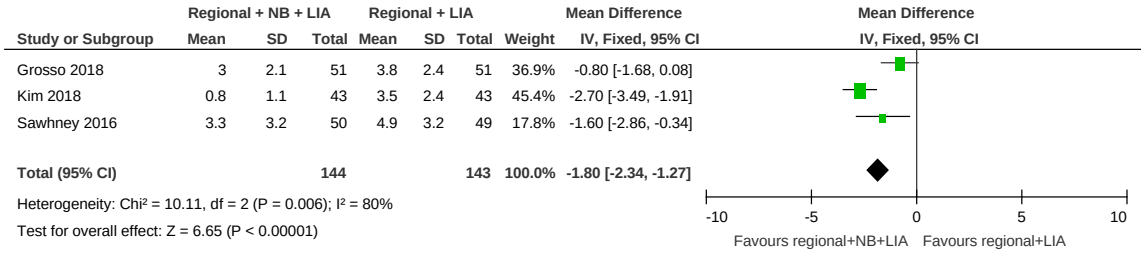


Figure 46: Postoperative use of analgesia

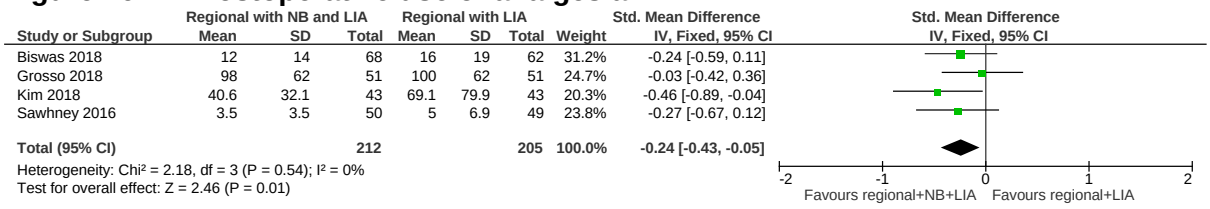


Figure 47: Length of stay

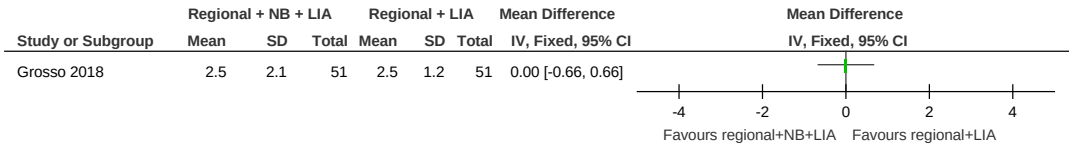


Figure 48: Nausea up to 30 days

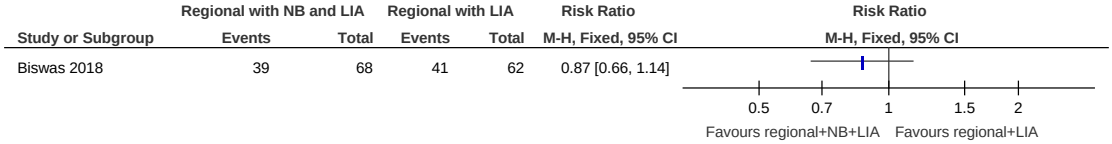
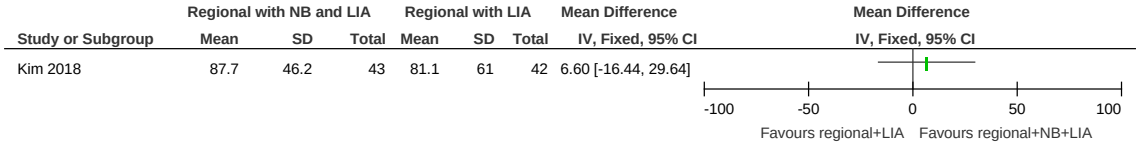


Figure 49: Mobilisation: distance walked on postoperative day 1



E.10 Regional anaesthesia with nerve block and LIA versus regional anaesthesia with nerve block

Figure 50: Postoperative pain up to 30 days

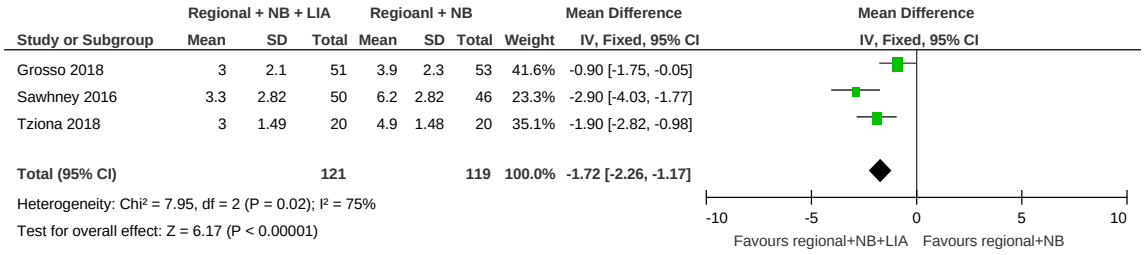


Figure 51: Postoperative use of analgesia

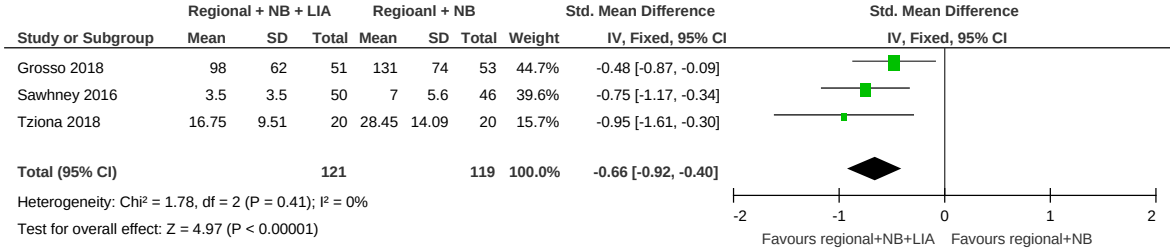


Figure 52: Length of stay

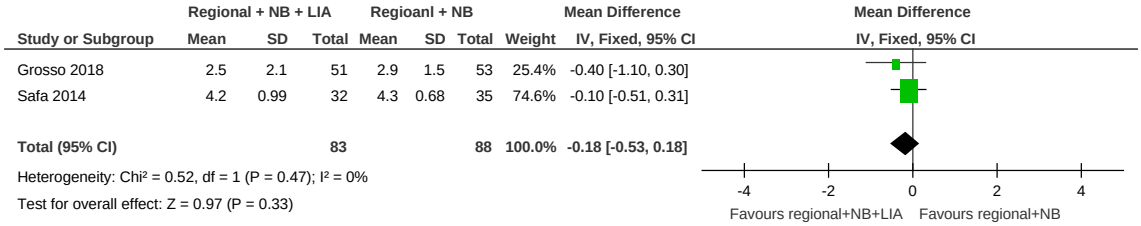


Figure 53: Nausea up to 30 days

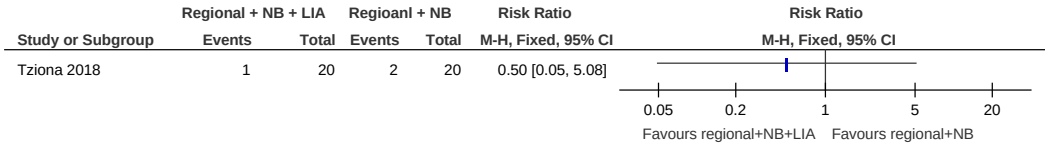
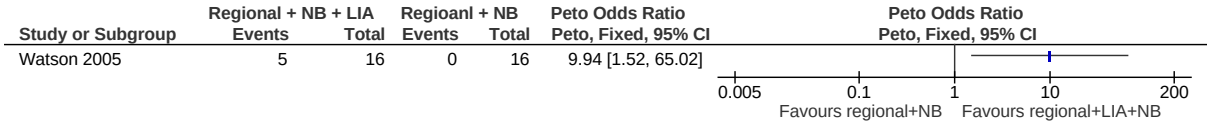


Figure 54: Mobilisation within 24 hours after surgery



E.11 1 General anaesthesia with LIA versus general anaesthesia

Figure 55: Thromboembolic complications up to 90 days

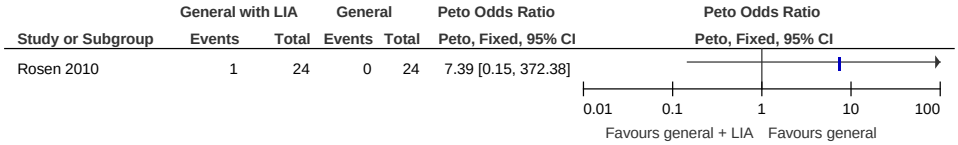


Figure 56: Length of stay

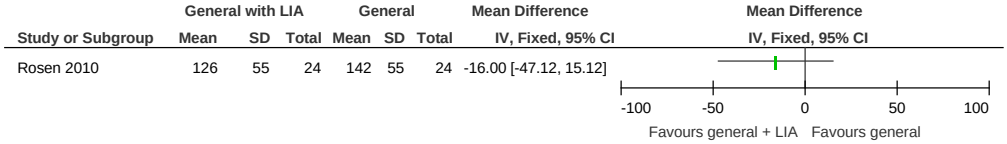
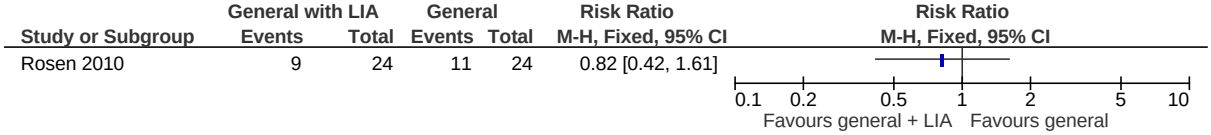


Figure 57: Nausea up to 30 days



E.12 2 General anaesthesia with nerve block versus general 3 anaesthesia

Figure 58: Postoperative pain up to 30 days

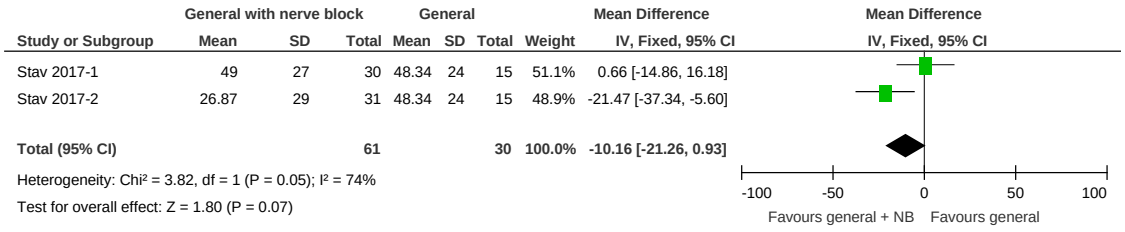
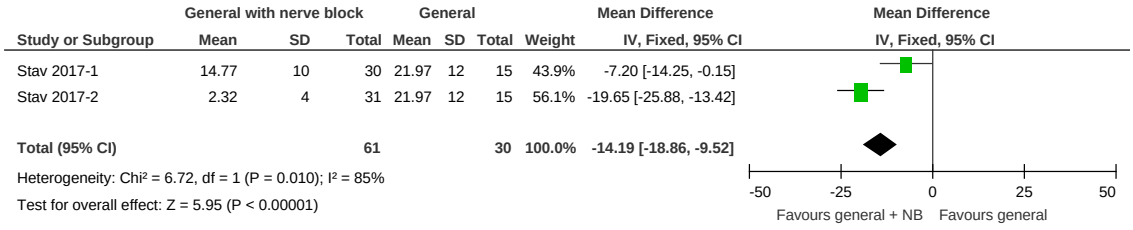


Figure 59: Postoperative use of analgesia



E.13 General anaesthesia with LIA versus general anaesthesia with nerve block

Figure 60: Postoperative use of analgesia

Study or Subgroup	General with LIA Mean	SD	Total	General with nerve block Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Rizk 2017	48.09	8.73	41	51.08	12.96	34	-2.99 [-8.10, 2.12]

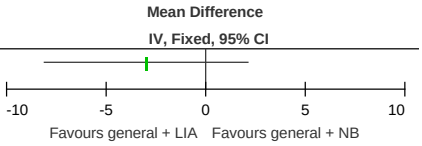


Figure 61: Length of stay

Study or Subgroup	General with LIA Mean	SD	Total	General with nerve block Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kastelik 2019	6.2	0.5	20	6.3	0.7	20	27.7%	-0.10 [-0.48, 0.28]
Rizk 2017	3.7	0.54	41	4	0.49	34	72.3%	-0.30 [-0.53, -0.07]
Total (95% CI)			**61**			**54**	**100.0%**	**-0.24 [-0.44, -0.05]**

Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)

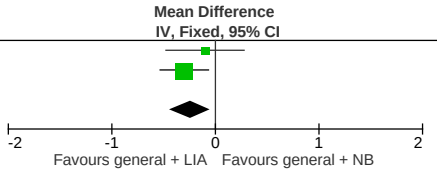
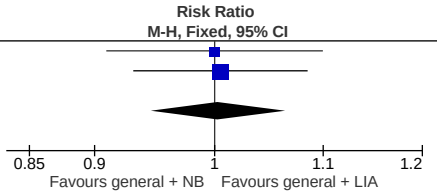


Figure 62: Mobilisation within 24 hours after surgery

Study or Subgroup	General with LIA Events	Total	General with nerve block Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kastelik 2019	20	20	20	20	36.2%	1.00 [0.91, 1.10]
Rizk 2017	40	41	33	34	63.8%	1.01 [0.93, 1.08]
Total (95% CI)		**61**		**54**	**100.0%**	**1.00 [0.95, 1.06]**
Total events	60		53			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)



E.14 General anaesthesia with nerve block and LIA versus general anaesthesia with LIA

Figure 63: Postoperative pain up to 30 days

Study or Subgroup	General + NB + LIA Mean	SD	Total	General + LIA Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Widmer 2012	2.4	0.9	27	2.5	0.9	28	-0.10 [-0.58, 0.38]

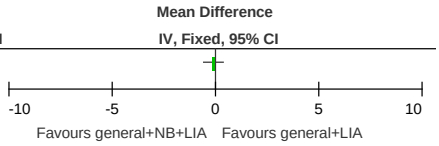


Figure 64: Thromboembolic complications up to 90 days

Study or Subgroup	General + NB + LIA Events	Total	General + LIA Events	Total	Risk Difference M-H, Fixed, 95% CI
Widmer 2012	0	27	0	28	0.00 [-0.07, 0.07]

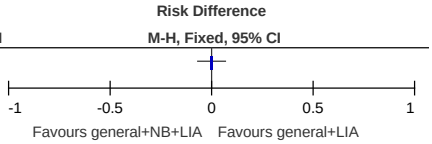
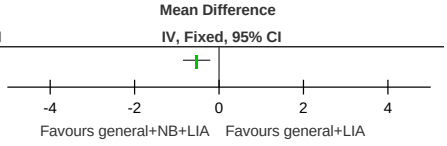


Figure 65: Postoperative use of analgesia

Study or Subgroup	General + NB + LIA Mean	SD	Total	General + LIA Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Widmer 2012	0.973	0.4267	27	1.502	0.7063	28	-0.53 [-0.84, -0.22]



Appendix F: GRADE tables

Table 23: 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 versus general	Control	Relative (95% CI)	Absolute		
Mortality (follow-up 2 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/133 (0.75%)	1/120 (0.83%)	RR 0.9 (0.06 to 14.27)	1 fewer per 1000 (from 8 fewer to 111 more)	⊕OOO VERY LOW	CRITICAL
Postoperative neurocognitive decline[3] (follow-up 1 weeks; measured with: Boston Naming; range of scores: 0-30; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	133	120	-	MD 0.3 lower (0.93 lower to 0.33 higher)	⊕⊕OO LOW	CRITICAL
Postoperative neurocognitive decline[3] (follow-up 1 weeks; measured with: Benton Visual Retention; range of scores: 0-10; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	133	120	-	MD 0 higher (0.48 lower to 0.48 higher)	⊕⊕OO LOW	CRITICAL
Postoperative neurocognitive decline[3] (follow-up 1 weeks; measured with: Wechsler Adult Intelligence Test; range of scores: 0-93; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	133	120	-	MD 1 lower (2.49 lower to 0.49 higher)	⊕⊕OO LOW	CRITICAL
Postoperative neurocognitive decline[3] (follow-up 1 weeks; assessed with: Delirium)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/133 (12%)	12/120 (10%)	RR 1.2 (0.59 to 2.44)	20 more per 1000 (from 41 fewer to 144 more)	⊕OOO VERY LOW	CRITICAL
Thromboembolic complications (follow-up prior to discharge; assessed with: DVT or PE)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	51/131 (38.9%)	49/119 (41.2%)	RR 0.93 (0.69 to 1.25)	29 fewer per 1000 (from 128 fewer to 103 more)	⊕OOO VERY LOW	CRITICAL
Length of stay (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	133	120	-	MD 0.6 lower (1.68 lower to 0.48 higher)	⊕⊕OO LOW	IMPORTANT
Mobilisation (measured with: time until transfer unassisted; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	133	120	-	MD 0.3 lower (1.08 lower to 0.48 higher)	⊕⊕OO LOW	IMPORTANT

1 [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 [2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 [2] Neurocognitive decline outcomes could not be meta-analysed because the 3 continuous outcomes came from the same study and the 4th outcome was dichotomous.

4

Table 24: Clinical evidence profile: Regional anaesthesia 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	Regional versus general with nerve block	Control	Relative (95% CI)	Absolute		
Postoperative pain (follow-up 1 days; measured with: Defence and Veterans Pain 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	44	47	-	MD 0.8 higher (0.17 lower to 1.77 higher)	⊕OOO VERY LOW	CRITICAL
Length of stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	47	-	MD 6 higher (6.76 lower to 18.76 higher)	⊕⊕OO LOW	IMPORTANT
Mobilisation (measured with: ambulating distance on postoperative day 1; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	41	-	MD 89 lower (144.35 to 33.65 lower)	⊕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.

1 **Table 25: Clinical evidence profile: Regional anaesthesia with LIA versus general anaesthesia with LIA**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regional with LIA versus general with LIA	Control	Relative (95% CI)	Absolute		
Thromboembolic complications (follow-up unclear; assessed with: Pulmonary embolism)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/60 (1.7%)	1/60 (1.7%)	RR 1 (0.06 to 15.62)	0 fewer per 1000 (from 16 fewer to 244 more)	⊕OOO VERY LOW	CRITICAL
Length of stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	60	60	-	MD 6 higher (2.51 to 9.49 higher)	⊕⊕OO LOW	IMPORTANT
Nausea (assessed with: Morning and afternoon of day after surgery)												
2	randomised trials	serious[1]	very serious[3]	no serious indirectness	very serious[2]	none	0/120 (0%)	17/120 (14.2%)	See comment[4]	140 fewer per 1000 (from 680 fewer to 400 more)[5]	⊕OOO VERY LOW	IMPORTANT
Mobilisation within 24 hours after surgery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/60 (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

[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] Analysis with risk difference due to low events rate
[5] Absolute effect calculated with risk difference

Table 26: Clinical evidence profile: Regional anaesthesia with nerve block 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**	**Regional with nerve block versus general with nerve block**	**Control**	**Relative (95% CI)**	**Absolute**		
Postoperative pain (follow-up 1 days; measured with: Defence and Veterans Pain Rating Scale; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	41	47	-	MD 0.4 lower (1.24 lower to 0.44 higher)	⊕⊕⊕O MODERATE	CRITICAL
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	41	47	-	MD 2 lower (13.84 lower to 9.84 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Mobilisation (measured with: ambulation distance on postoperative day 1; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	47	-	MD 17 higher (39.45 lower to 73.45 higher)	⊕⊕⊕O MODERATE	IMPORTANT

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

Table 27: Clinical evidence profile: General and regional anaesthesia versus general anaesthesia and nerve block

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General and regional versus general and nerve block	Control	Relative (95% CI)	Absolute		
Postoperative pain (follow-up during hospital recovery; assessed with: no pain on movement)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/29 (79.3%)	16/30 (53.3%)	RR 1.49 (1.01 to 2.18)	261 more per 1000 (from 5 more to 629 more)	⊕OOO VERY LOW	CRITICAL
Nausea/Vomiting (follow-up prior to hospital discharge)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/30 (20%)	4/30 (13.3%)	RR 1.5 (0.47 to 4.78)	67 more per 1000 (from 71 fewer to 504 more)	⊕OOO VERY LOW	IMPORTANT
Mobilisation within 24 hours after surgery (assessed with: Ability to perform a straight-leg raise)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/30 (13.3%)	7/30 (23.3%)	RR 0.57 (0.19 to 1.75)	100 fewer per 1000 (from 189 fewer to 175 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.

1 **Table 28: 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 with LIA versus regional	Control	Relative (95% CI)	Absolute		
Postoperative pain (follow-up 0-1 days; measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
6[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	222	191	-	MD 0.66 lower (1.13 to 0.2 lower)	⊕⊕OO LOW	CRITICAL
Postoperative pain (follow-up while still admitted in hospital; assessed with: Person removed from study due to pain)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/27 (0%)	3/29 (10.3%)	Peto OR 0.13 (0.01 to 1.35)	90 fewer per 1000 (from 102 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Thromboembolic complications (follow-up unclear; assessed with: Pulmonary embolism)												
2	randomised trials	serious[2]	serious[4]	no serious indirectness	very serious[3]	none	1/125 (0.8%)	1/125 (0.8%)	Peto OR 1 (0.14 to 7.01)	0 fewer per 1000 (from 7 fewer to 48 more)	⊕OOO VERY LOW	CRITICAL
Hospital readmissions (follow-up within 6 weeks of surgery; assessed with: Treatment for stiffness or reoperation)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/200 (3%)	10/200 (5%)	RR 0.62 (0.24 to 1.61)	19 fewer per 1000 (from 38 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL

Postoperative use of analgesia (follow-up 1 days; assessed with: Use of rescue medication)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/50 (36%)	23/50 (46%)	RR 0.78 (0.49 to 1.26)	101 fewer per 1000 (from 235 fewer to 120 more)	⊕OOO VERY LOW	IMPORTANT
Postoperative use of analgesia (follow-up at varying in-hospital time points; measured with: PCA use or narcotic consumption; Better indicated by lower values)												
6[1]	randomised trials	serious[2]	very serious[4]	no serious indirectness	serious[3]	none	209	210	-	SMD 0.34 lower (0.54 to 0.15 lower)	⊕OOO VERY LOW	IMPORTANT
Length of stay (Better indicated by lower values)												
3	randomised trials	very serious[2]	very serious[4]	no serious indirectness	serious[3]	none	87	86	-	MD 0.24 higher (1.54 lower to 2.02 higher)	⊕OOO VERY LOW	IMPORTANT
Nausea (or vomiting in 1 study) (follow-up varying in-hospital time points)												
5	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	31/151 (20.5%)	21/124 (16.9%)	RR 0.90 (0.56 to 1.45)	17 fewer per 1000 (from 75 fewer to 76 more)	⊕OOO VERY LOW	IMPORTANT

[1] 2 intervention groups from Han 2007 utilised in this analysis. Comparator group halved in size to prevent double counting.
[2] 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.
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis.

1 **Table 29: 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 with nerve block versus regional	Control	Relative (95% CI)	Absolute		
Postoperative pain (follow-up 2 hours after surgery or postoperative day 1; measured with: Defence and Veterans Pain Rating Scale or VAS; range of scores: 0-10; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	61	64	-	MD 1.34 lower (2.01 to 0.68 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Postoperative pain (follow-up postoperative day 1; assessed with: VAS >/= 6)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/41 (4.9%)	12/39 (30.8%)	RR 0.16 (0.04 to 0.66)	258 fewer per 1000 (from 105 fewer to 295 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Postoperative use of analgesia (follow-up 1 days; measured with: Accumulated morphine consumption ; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD 10.08 lower (17.88 to 2.28 lower)	⊕⊕OO LOW	IMPORTANT
Length of stay (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	41	44	-	MD 8 lower (16.5 lower to 0.5 higher)	⊕⊕⊕O MODERATE	IMPORTANT

Nausea (follow-up while in hospital)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/20 (0%)	0/20 (0%)	See comment[4]	0 fewer per 1000 (from 90 fewer to 90 more)[5]	⊕⊕OO LOW	IMPORTANT
Mobilisation: (follow-up mean 1 days; measured with: Ambulation distance on postoperative day 1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41	44	-	MD 89 higher (33.65 to 144.35 higher)	⊕⊕OO 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 one increment for imprecision as it is a small study with no events.
[4] Analysed using risk difference due to zero events in both groups
[5] Absolute effect calculated using the risk difference

Table 30: 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 with LIA versus regional with nerve block**	**Control**	**Relative (95% CI)**	**Absolute**		
Postoperative pain (follow-up all at some point before the end of postoperative day 1; measured with: VAS or NRS; range of scores: 0-10; Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	160	159	-	MD 0.95 lower (1.5 to 0.39 lower)	⊕⊕OO LOW	CRITICAL

Postoperative pain (measured with: time to onset; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100	100	-	MD 6.9 lower (9.34 to 4.46 lower)	⊕⊕⊕O MODERATE	CRITICAL
Thromboembolic complications (follow-up unclear; assessed with: DVT)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/35 (0%)	1/35 (2.9%)	Peto OR 0.14 (0.0 to 6.82)	25 fewer per 1000 (from 29 fewer to 166 more)	⊕OOO VERY LOW	CRITICAL
Hospital readmissions (follow-up mean 4 weeks; assessed with: For irrigation, debridement and polythene exchange)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/20 (5%)	0/20 (0%)	Peto OR 7.39 (0.15 to 372.38)	50 more per 1000 (from 80 fewer to 180 more)[3]	⊕OOO VERY LOW	CRITICAL
Postoperative use of analgesia (follow-up 48 hours after surgery; measured with: Number of suppositories used; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100	100	-	MD 0.1 higher (0.27 lower to 0.47 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Postoperative use of analgesia (follow-up varying time points no later than postoperative day 3; measured with: Usage in mg; Better indicated by lower values)												
5	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[2]	none	195	194	-	SMD 0.29 lower (0.61 lower to 0.03 higher)	⊕OOO VERY LOW	IMPORTANT
Length of stay (Better indicated by lower values)												

4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	109	-	MD 0.29 lower (0.61 lower to 0.03 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Nausea (and vomiting in one paper) (follow-up unclear)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/120 (10%)	9/120 (7.5%)	RR 1.32 (0.59 to 2.94)	24 more per 1000 (from 31 fewer to 146 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] Absolute effect calculated using the risk difference. RD: 0.05 [-0.08, 0.18]
[4] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.

Table 31: Clinical evidence profile: Regional anaesthesia with nerve block and LIA versus regional anaesthesia with LIA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Regional with nerve block and LIA versus regional with LIA**	**Control**	**Relative (95% CI)**	**Absolute**		
Postoperative pain (follow-up in-hospital period; assessed with: Requiring rescue IV PCA)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/68 (33.8%)	26/62 (41.9%)	RR 0.81 (0.52 to 1.26)	80 fewer per 1000 (from 201 fewer to 109 more)	⊕OOO VERY LOW	CRITICAL
Postoperative pain (follow-up varying within 1 day of surgery ; measured with: VAS or NRS; range of scores: 0-10; Better indicated by lower values)												

3	randomised trials	serious[1]	very serious[3]	no serious indirectness	serious[2]	none	144	143	-	MD 1.8 lower (2.34 to 1.27 lower)	⊕OOO VERY LOW	
Postoperative use of analgesia (follow-up varying within 3 days of surgery; measured with: Opioid consumption; Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	212	205	-	SMD 0.24 lower (0.43 to 0.05 lower)	⊕⊕OO LOW	IMPORTANT
Length of stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	51	-	MD 0 higher (0.66 lower to 0.66 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Nausea or vomiting (follow-up while in hospital)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/68 (57.4%)	41/62 (66.1%)	RR 0.87 (0.66 to 1.14)	86 fewer per 1000 (from 225 fewer to 93 more)	⊕⊕OO LOW	IMPORTANT
Mobilisation (measured with: Distance walked on postoperative day 1; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	43	42	-	MD 6.6 higher (16.44 lower to 29.64 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 by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.

1 **Table 32: Clinical evidence profile: Regional anaesthesia with nerve block and 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 with nerve block and LIA versus regional with nerve block**	**Control**	**Relative (95% CI)**	**Absolute**		
Postoperative pain (follow-up varies within 1 day surgery ; measured with: VAS or NRS; range of scores: 0-10; Better indicated by lower values)												
3	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	121	119	-	MD 1.72 lower (2.26 to 1.17 lower)	⊕OOO VERY LOW	CRITICAL
Postoperative use of analgesia (follow-up varies within 3 days of surgery; measured with: Opioid consumption; Better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	121	119	-	SMD 0.66 lower (0.92 to 0.4 lower)	⊕⊕OO 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	83	88	-	MD 0.18 lower (0.53 lower to 0.18 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Nausea (follow-up within 24 hours of surgery)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/20 (5%)	2/20 (10%)	RR 0.5 (0.05 to	50 fewer per 1000 (from 95 fewer to	⊕OOO VERY LOW	IMPORTANT

									5.08)	408 more)		
Mobilisation within 24 hours after surgery												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/16 (31.3%)	0/16 (0%)	RR 9.94 (1.52 to 65.02)	310 more per 1000 (from 80 more to 550 more)[4]	⊕⊕⊕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 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Absolute effect calculated using the risk difference. RD: 0.31 [0.08, 0.55]]

Table 33: 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 with LIA versus general**	**Control**	**Relative (95% CI)**	**Absolute**		
Thromboembolic complications (follow-up unclear; assessed with: Proximal DVT)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/24 (4.2%)	0/24 (0%)	RR 7.39 (0.15 to 372.38)	40 more per 1000 (from 70 fewer to 150 more)[3]	⊕OOO VERY LOW	CRITICAL
Length of stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	24	-	MD 16 lower (47.12 lower to 15.12 higher)	⊕⊕OO LOW	IMPORTANT

Nausea (follow-up unclear)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/24 (37.5%)	11/24 (45.8%)	RR 0.82 (0.42 to 1.61)	82 fewer per 1000 (from 266 fewer to 280 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] Absolute effect calculated using the risk difference. RD: 0.04 (-0.07, 0.15)

Table 34: Clinical evidence profile: General anaesthesia with nerve block versus general anaesthesia

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**General with nerve block versus general**	**Control**	**Relative (95% CI)**	**Absolute**		
Postoperative pain (measured with: VAS at rest on postoperative day 0; range of scores: 0-100; Better indicated by lower values)												
2[1]	randomised trials	very serious[2]	serious[3]	no serious indirectness	serious[4]	none	61	30	-	MD 10.34 lower (32.03 lower to 11.35 higher)	⊕OOO VERY LOW	CRITICAL
Postoperative use of analgesia (measured with: Morphine consumption via PCA in mg on postoperative day 0; Better indicated by lower values)												
2[1]	randomised trials	very serious[2]	very serious[3]	no serious indirectness	no serious imprecision	none	61	30	-	MD 13.54 lower (25.74 to 1.34 lower)	⊕OOO VERY LOW	IMPORTANT

[1] Both results from the same study but utilising different treatment groups
[2] 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.

[3] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects model used.
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 35: 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 with LIA versus general with nerve block	Control	Relative (95% CI)	Absolute		
Postoperative use of analgesia (follow-up 48 hours after surgery; measured with: Opioid consumption; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41	34	-	MD 2.99 lower (8.1 lower to 2.12 higher)	⊕OOO VERY LOW	IMPORTANT
Length of stay (Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61	54	-	MD 0.24 lower (0.44 to 0.05 lower)	⊕OOO VERY LOW	IMPORTANT
Mobilisation 24 or 31 hours after surgery (follow-up postoperative day 1; assessed with: Varying: walking 10m or mobilised to stand)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60/61 (98.4%)	53/54 (98.1%)	RR 1.01 (0.93 to 1.08)	10 more per 1000 (from 69 fewer to 79 more)	⊕⊕OO 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.

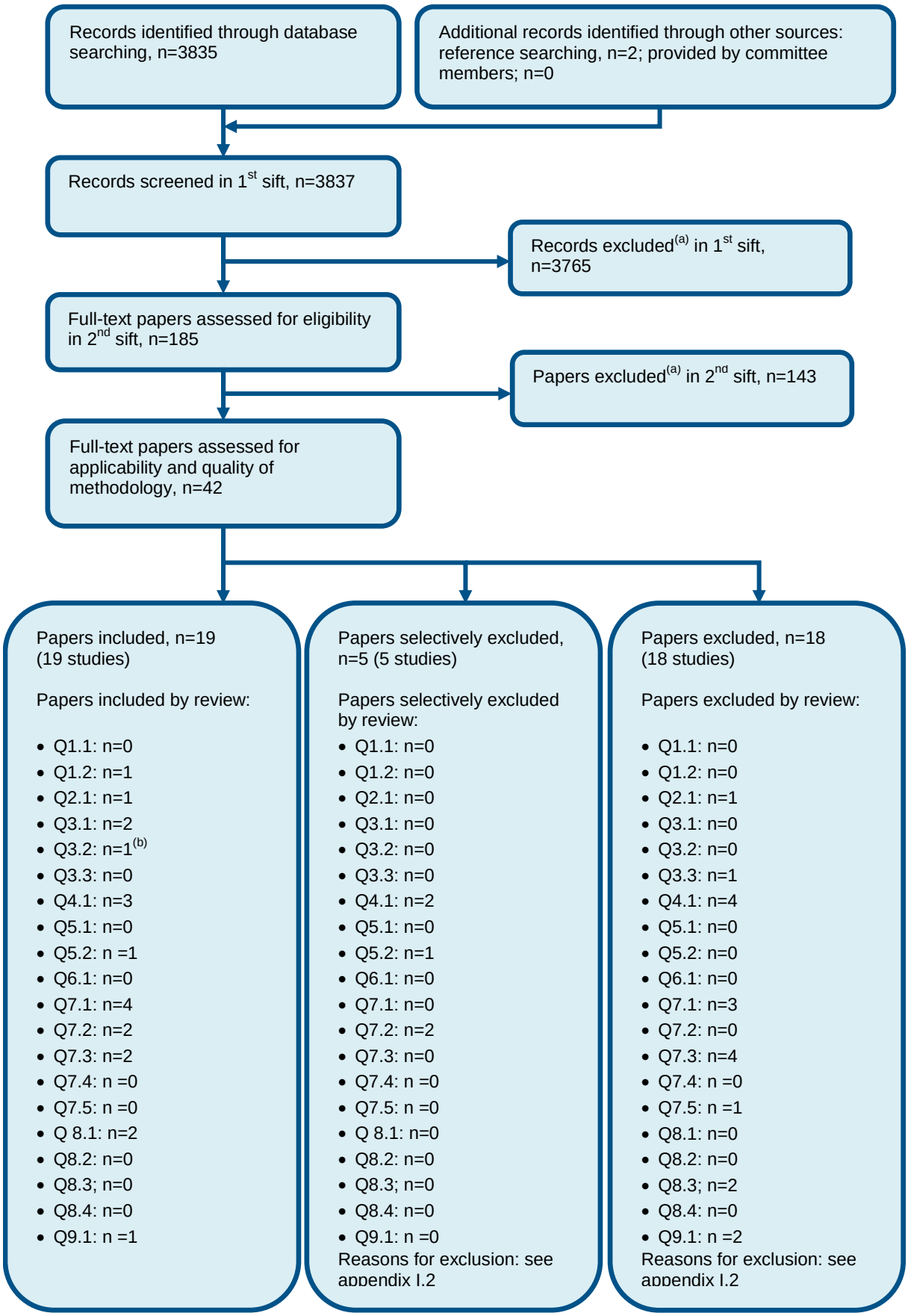
Table 36: Clinical evidence profile: General anaesthesia with nerve block and LIA versus general anaesthesia with LIA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	General with nerve block and LIA versus general with LIA	Control	Relative (95% CI)	Absolute		
Postoperative pain (follow-up 24 hours after surgery; measured with: Unclear scale; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27	28	-	MD 0.1 lower (0.58 lower to 0.38 higher)	⊕OOO VERY LOW	CRITICAL
Thromboembolic complications (follow-up while in hospital; assessed with: Thromboembolic events)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/27 (0%)	0/28 (0%)	See comment[4]	0 fewer per 1000 (from 70 fewer to 70 more)[5]	⊕OOO VERY LOW	CRITICAL
Postoperative use of analgesia (follow-up within 24 hours of surgery; measured with: Fentanyl use via PCA; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27	28	-	MD 0.53 lower (0.84 to 0.22 lower)	⊕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 one increment for imprecision as it is a small study with no events.
[4] Analysis by risk difference due to zero events in both treatment arms
[5] Absolute effect calculated using the risk difference

Appendix G: Health economic evidence selection

Figure 66: Flow chart of health economic study selection for the guideline



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

1

Appendix H: Health economic evidence tables

Study	Marques 2015[170]			
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 TKR **Perspective:** UK NHS **Follow-up:** 12 months post operatively **Discounting:** Costs: N/A; Outcomes: N/A	**Population:** People who have undergone primary TKR **Cohort characteristics:** n=316 Start age: NR Male: NR **Intervention 1:** Standard anaesthetic regimen which consisted of a femoral nerve block in addition to spinal or general anaesthesia **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 saved £77 per person (95% CI: -£451 to £296; p=0.68) **Currency & cost year:** 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): Intervention 2 gave 0.009 more QALYs (95% CI: -0.030 to 0.049; p=0.64) **Inpatient admissions after discharge (total):** Intervention 1: 110/159 (69.2%)[(a)] Intervention 2: 103/157 (65.6%)	Intervention 2 dominates Intervention 1 **Analysis of uncertainty:** A probabilistic sensitivity analysis investigating 4 scenarios was conducted; excluding PSS costs, using macro-costed prescribed medications, 50% higher local inpatient costs and 50% lower local inpatient costs. Intervention 2 remained dominant in all instances. In the base case there was a 60% probability 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 142/316 (45%) of participants. The final dataset therefore included imputed missing costs and outcome data; outcomes from a single RCT excluded from the clinical review as it is not possible to tell if patients received general or regional anaesthesia.				

Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious 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; PSS: personal social services; QALYs= quality-adjusted life years; TKR: total knee 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

(d) This study was excluded from the clinical review as it was not possible to determine if participants had received spinal or general anaesthesia. It has been included as economic evidence as it may still provide useful cost information for the committee

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 37) 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[196] 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 knee replacements. However, a 24 hour time horizon may be the most appropriate when considering acute post-operative outcomes (for example, pain, post-operative nausea and vomiting). A longer time horizon of 10 days to 30 days may be most appropriate to account for the possible effect of anaesthetic choice on adverse clinical outcomes (for example post-operative morbidity and mortality). Lastly, an even longer time horizon would be needed to account for long term outcomes (such as chronic pain, opioid dependence and range of motion). However, in line with the pain score outcome included in the protocol, the maximum effect horizon included in the analysis was 30 days. The different QALY gains calculated as outlined above were then substituted into the QALY equation with the different time horizons (24 hours, 3 days, 10 days and 30 days). The equation was then rearranged to find the gain in HRQoL gain needed to be cost effective at a threshold of £20,000 under each scenario.

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

Therefore:

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

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

Table 37 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 37: 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)[49]; CG124[196]

(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[196]

I.26 Results

The gain in QALY and gain in HRQoL needed under a range of different scenarios is shown in Table 38. For a number of scenarios; particularly when the time to administer was 30 minutes, the intervention effect was 24 hours and when theatre time was included; the likelihood of nerve blocks being cost effective was impossible given that the gain in HRQoL needed was greater than 1. When the assumptions were softened to the middle values, the gain in HRQoL was often not impossible (the gain needed was less than 1) but improbable. Finally, when time to administer was 5 minutes, the intervention effect was 30 days and when theatre time was excluded, the gain in HRQoL and therefore cost-effectiveness was more realistic.

Table 38: 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 time horizon is longer (as discussed, the most appropriate time horizon 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 the addition of a nerve block to LIA and regional or general anaesthesia.

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 39: Studies excluded from the clinical review

Study	Exclusion reason

Study	Exclusion reason
Abdallah 2014[1]	Inappropriate comparison
Affas 2011[2]	Incorrect interventions
Affas 2012[3]	Incorrect interventions
Aksoy 2013[4]	Unclear if the study population is people undergoing primary knee arthroplasty
Ali 2015[6]	Unclear if the study population is people undergoing primary knee arthroplasty
Allen 1998[7]	Unclear if the study population is people undergoing primary knee arthroplasty
Al-zahrani 2015[5]	Inappropriate comparison
Amundson 2017[8]	Incorrect interventions
Anastase 2014[9]	Inappropriate comparison
Andersen 2008[13]	Inappropriate comparison
Andersen 2010[12]	Unclear if the study population is people undergoing primary knee arthroplasty
Andersen 2010[11]	Incorrect interventions
Andersen 2013[10]	Unclear if the study population is people undergoing primary knee arthroplasty
Angers 2019[14]	Inappropriate comparison
Ashraf 2013[15]	Unable to obtain
Axelsson 2005[18]	Unclear if the study population is people undergoing primary knee arthroplasty
Baldini 2006[19]	Conference abstract
Bali 2016[20]	Unclear if the study population is people undergoing primary knee arthroplasty
Baranovic 2011[21]	Inappropriate comparison
Barastegui 2017[22]	Unclear if the study population is people undergoing primary knee arthroplasty
Barrington 2005[23]	Inappropriate comparison
Beaupre 2012[24]	Observational study without adjustment for confounding
Bergeron 2009[25]	Incorrect interventions
Bergese 2012[26]	Inappropriate comparison
Bianconi 2003[27]	Not review population
Binici bedir 2014[28]	Incorrect interventions
Busch 2006[30]	Unclear if the study population is people undergoing primary knee arthroplasty
Campbell 2008[31]	Unclear if the study population is people undergoing primary knee arthroplasty
Canakci 2017[32]	Unclear if the study population is people undergoing primary knee arthroplasty
Canata 2016[33]	Incorrect interventions
Carli 2010[34]	Incorrect interventions
Chan 2012[37]	Incorrect interventions
Chan 2013[35]	Incorrect interventions
Chandy 2019[38]	Incorrect interventions
Chaubey 2017[39]	Unclear if the study population is people undergoing primary knee arthroplasty
Chaumeron 2013[40]	Incorrect interventions

Study	Exclusion reason
Chinachoti 2012[41]	Unclear if the study population is people undergoing primary knee arthroplasty
Choi 2006[42]	Not in English
Chong 2017[44]	Systematic review with different inclusion criteria however included studies were checked for this review
Chu 2006[45]	Incorrect interventions
Chun 2009[46]	Not in English
Churadze 2013[47]	Not in English
Cip 2016[48]	Observational study without adjustment for confounding factors
D'ambrosio 2015[50]	Incorrect interventions
De andres 1993[52]	Not review population
Den hartog 2015[53]	Not review population
Deng 2017[54]	Not in English
Dong 2016[56]	Systematic review with different inclusion criteria however included studies were checked for this review
Drakeford 1991[57]	Unclear if the study population is people undergoing primary knee arthroplasty
Duggal 2015[58]	Observational study without adjustment for confounding factors
Edwards 1992[59]	Unclear if the study population is people undergoing primary knee arthroplasty
Ekin 2013[60]	Not in English
Eledjam 2002[61]	Not review population
Eskandr 2016[62]	Unclear if the study population is people undergoing primary knee arthroplasty
Essving 2009[64]	Unclear if the study population is people undergoing primary knee arthroplasty
Essving 2010[65]	Unclear if the study population is people undergoing primary knee arthroplasty
Essving 2011[63]	Unclear if the study population is people undergoing primary knee arthroplasty
Etches 1995[66]	Not review population
Ezri 2006[67]	Inappropriate comparison
Fan 2015[69]	Systematic review with different inclusion criteria however included studies were checked for this review
Fan 2016[68]	Incorrect interventions
Fenten 2018[70]	Incorrect interventions
Finn 2016[71]	Observational study without adjustment for confounding factors
Frassanito 2010[72]	Incorrect interventions
Fu 2017[73]	Systematic review with different inclusion criteria however included studies were checked for this review
Gallardo 2011[74]	Not in English
Ganapathy 1997[75]	Not review population
Ganapathy 1999[76]	Unclear if the study population is people undergoing primary knee arthroplasty
Gandhi 2011[77]	Inappropriate comparison
Gao 2017[78]	Systematic review with different inclusion criteria however included studies were checked for this review
Gao 2017[79]	Not in English

Study	Exclusion reason
Gao 2017[80]	Not in English
Ghoneim 1988[81]	Not review population
Gi 2014[82]	Unclear if the study population is people undergoing primary knee arthroplasty
Gomez-cardero 2010[83]	Unclear if the study population is people undergoing primary knee arthroplasty
Gonano 2006[84]	Not review population
Good 2007[85]	Unclear if the study population is people undergoing primary knee arthroplasty
Grabowska-gawel 2003[87]	Not in English
Grace 1995[88]	Unclear if the study population is people undergoing primary knee arthroplasty
Guo 2015[90]	Not in English
Gwam 2017[91]	Observational study without adjustment for confounding factors
Hadzic 2005[92]	Not review population
Hadzic 2016[93]	Inappropriate comparison
Han 2006[94]	Not in English
Hanson 2016[96]	Observational study without adjustment for confounding factors
Harsten 2013[97]	Incorrect interventions
Hartrick 2006[99]	Unclear if the study population is people undergoing primary knee arthroplasty
Hartrick 2011[100]	Incorrect interventions
Hebl 2008[101]	Not review population
Hidaka 2005[102]	Not review population
Himmelseher 2001[103]	Unclear if the study population is people undergoing primary knee arthroplasty
Hirst 1996[105]	Unclear if the study population is people undergoing primary knee arthroplasty
Horasanli 2010[106]	Unclear if the study population is people undergoing primary knee arthroplasty
Horn 2015[107]	Observational study without adjustment for confounding factors
Hou 2018[108]	Not in English
Hsu 2013[109]	Not review population
Hunt 2009[110]	Unclear if the study population is people undergoing primary knee arthroplasty
Ilfeld 2008[112]	Incorrect interventions
Ilfeld 2009[114]	Incorrect interventions
Ilfeld 2010[113]	Incorrect interventions
Ilfeld 2011[115]	Incorrect interventions
Ilfeld 2017[111]	Incorrect interventions
Ishida 2016[116]	Observational study without adjustment for confounding factors
Jenstrup 2012[117]	Incorrect interventions
Jeong 2011[118]	Not in English
Johnson 2011[119]	Unclear if the study population is people undergoing primary knee arthroplasty
Jones 1990[120]	Not review population
Jorgensen 1991[121]	Population includes people undergoing revision surgery
Jun 2015[122]	Not in English

Study	Exclusion reason
Kacha 2018[123]	Not review population
Kadic 2009[124]	Incorrect interventions
Kadic 2016[125]	Incorrect interventions
Kaloul 2004[126]	Inappropriate comparison
Kampe 2002[127]	Unclear if the study population is people undergoing primary knee arthroplasty
Kampe 2003[128]	Unclear if the study population is people undergoing primary knee arthroplasty
Kampitak 2018[130]	Incorrect interventions
Kampitak 2018[129]	Unclear if the study population is people undergoing primary knee arthroplasty
Kandikatu 2006[131]	Unable to obtain
Kao 2015[132]	Observational study without adjustment for confounding factors
Karlsen 2017[133]	Systematic review with different inclusion criteria however included studies were checked for this review
Khan 2018[137]	Unclear if the study population is people undergoing primary knee arthroplasty
Khan 2018[136]	Unclear if the study population is people undergoing primary knee arthroplasty
Kilickaya 2016[138]	Unclear if the study population is people undergoing primary knee arthroplasty
Kirkness 2016[140]	Unclear if the study population is people undergoing primary knee arthroplasty
Kovalak 2015[141]	Unclear if the study population is people undergoing primary knee arthroplasty
Krenzel 2009[142]	Incorrect interventions
Kudoh 2004[143]	Unclear if the study population is people undergoing primary knee arthroplasty
Kurosaka 2016[144]	Unclear if the study population is people undergoing primary knee arthroplasty
Kutzner 2015[145]	Not in English
Lee 2007[146]	Not in English
Lee 2009[148]	Varying preoperative and postoperative pain relief between treatment groups
Lee 2012[147]	Unclear if the study population is people undergoing primary knee arthroplasty
Lee 2012[149]	Observational study without adjustment for confounding factors
Leung 2018[150]	Unclear if the study population is people undergoing primary knee arthroplasty
Li 2017[151]	Unclear anaesthesia utilised
Liu 2013[152]	Not in English
Liu 2014[153]	Unclear if the study population is people undergoing primary knee arthroplasty
Liu 2015[154]	Observational study without adjustment for confounding factors
Long 2006[155]	Unclear if the study population is people undergoing primary knee arthroplasty
Looseley 2013[156]	Unable to obtain
Lopez gonzalez 2012[157]	Not in English
Lorenzini 2002[158]	Not review population

Study	Exclusion reason
Lu 2014[159]	Not in English
Lu 2017[160]	Incorrect interventions
Lund 2011[161]	Incorrect study design
Ma 2016[162]	Systematic review with different inclusion criteria however included studies were checked for this review
Machi 2015[163]	Inappropriate comparison
Macrinici 2016[164]	Conference poster
Macrinici 2017[165]	Inappropriate comparison
Mahadevan 2010[166]	Unable to obtain
Mahadevan 2012[167]	Inappropriate comparison
Mandal 2011[168]	Not review population
Mangar 2014[169]	Inappropriate comparison
Martikainen 2001[171]	Not review population
Mas 2011[172]	Unclear if the study population is people undergoing primary knee arthroplasty
Masoudifar 2012[173]	Not in English
Mcbeath 1995[174]	Observational study without adjustment for confounding factors
Mcdonald 2016[175]	Incorrect interventions
Mcnamee 2002[177]	Inappropriate comparison
Meftah 2012[178]	Inappropriate comparison
Mei 2015[179]	Systematic review with different inclusion criteria however included studies were checked for this review
Mejia-terrazas 2007[180]	Not in English
Minkowitz 2013[182]	Unclear if the study population is people undergoing primary knee arthroplasty
Misiran 2013[183]	Unclear if the study population is people undergoing primary knee arthroplasty
Mistraletti 2006[184]	Inappropriate comparison
Moghtadaei 2013[187]	Not in English
Mont 2018[188]	Inappropriate comparison
Morin 2005[189]	Unclear if the study population is people undergoing primary knee arthroplasty
Mouzopoulos 2014[190]	Unable to obtain
Mulford 2016[191]	Inappropriate comparison
Nader 2012[193]	Inappropriate comparison
Nader 2016[192]	Unclear if the study population is people undergoing primary knee arthroplasty
Nagafuchi 2015[194]	Unclear if the study population is people undergoing primary knee arthroplasty
Ng 2001[198]	Unclear if the study population is people undergoing primary knee arthroplasty
Ng 2012[197]	Incorrect study design
Nielsen 1990[199]	Primary and revision surgeries included in the trial
Nielson 1990[200]	Unclear if the study population is people undergoing primary knee arthroplasty
Niemi 1996[202]	Not review population
Niskanen 2005[203]	Incorrect interventions
Oberhofer 2011[204]	Not review population

Study	Exclusion reason
Olive 2015[205]	Inappropriate comparison
Ong 2010[206]	Unclear if the study population is people undergoing primary knee arthroplasty
Ortiz-gomez 2017[207]	Unclear if the study population is people undergoing primary knee arthroplasty
Ozen 2006[208]	Unclear if the study population is people undergoing primary knee arthroplasty
Ozhan 2012[209]	Not in English
Ozkan 2013[210]	Unclear if the study population is people undergoing primary knee arthroplasty
Panwar 2017[211]	Unclear if the study population is people undergoing primary knee arthroplasty
Park 2006[212]	Not in English
Park 2014[213]	Not in English
Parvataneni 2007[214]	Not review population
Peng 2014[216]	Inappropriate comparison
Peng 2015[215]	Not in English
Pinsornsak 2017[217]	Inappropriate comparison
Raimer 2007[218]	Unclear if the study population is people undergoing primary knee arthroplasty
Raj 1987[219]	Inappropriate comparison
Rajeev 2016[220]	Observational study without adjustment for confounding factors
Reeves 2009[221]	Unclear if the study population is people undergoing primary knee arthroplasty
Reinhardt 2014[222]	Inappropriate comparison
Ren 2015[223]	Not in English
Riad 2002[224]	Systematic review with different inclusion criteria however included studies were checked for this review
Romberg 2007[226]	Unclear if the study population is people undergoing primary knee arthroplasty
Rosseland 1999[228]	Not review population
Rousseau-saine 2018[229]	Incorrect interventions
Runge 2018[231]	Incorrect interventions
Safa 2011[233]	Unable to obtain
Saglik 2015[234]	Not review population
Sahin 2014[235]	Unclear if the study population is people undergoing primary knee arthroplasty
Sakai 2016[237]	Incorrect interventions
Sankineani 2018[238]	Incorrect interventions
Santiveri papiol 2009[239]	Not in English
Sarridou 2015[240]	Unclear if the study population is people undergoing primary knee arthroplasty
Sathitkarnmanee 2014[241]	Unclear if the study population is people undergoing primary knee arthroplasty
Sato 2011[243]	Observational study without adjustment for confounding factors
Sato 2014[242]	Inappropriate comparison
Scardino 2018[245]	Observational study without adjustment for confounding factors
Schmidt 2009[246]	Observational study without adjustment for confounding factors

Study	Exclusion reason
Schultz 1991[247]	Unclear if the study population is people undergoing primary knee arthroplasty
Schumer 2018[248]	Inappropriate comparison
Seet 2006[249]	Unclear if the study population is people undergoing primary knee arthroplasty
Serpell 1991[250]	Unclear if the study population is people undergoing primary knee arthroplasty
Shah 2014[251]	Inappropriate comparison
Shah 2015[252]	Inappropriate comparison
Shanthanna 2012[253]	Unclear if the study population is people undergoing primary knee arthroplasty
Sharrock 1992[254]	Unable to obtain
Sharrock 1993[255]	Unable to obtain
Sharrock 1997[256]	Subgroup analysis from an included study
Shin 2018[257]	Unclear if the study population is people undergoing primary knee arthroplasty
Shum 2009[258]	Unclear if the study population is people undergoing primary knee arthroplasty
Sigirci 2017[259]	Unclear if the study population is people undergoing primary knee arthroplasty
Silvasti 2001[260]	Incorrect interventions
Singelyn 1998[261]	Unclear if the study population is people undergoing primary knee arthroplasty
Singelyn 2000[262]	Unclear if the study population is people undergoing primary knee arthroplasty
Sinha 2012[263]	Inappropriate comparison
Sites 2004[264]	Unclear if the study population is people undergoing primary knee arthroplasty
Sitsen 2007[265]	Unclear if the study population is people undergoing primary knee arthroplasty
Smet 2008[266]	Not review population
Song 2016[268]	Unclear if the study population is people undergoing primary knee arthroplasty
Sorensen 2016[269]	Unclear if the study population is people undergoing primary knee arthroplasty
Spangehl 2015[270]	Unclear if the study population is people undergoing primary knee arthroplasty
Spreng 2010[271]	Unclear if the study population is people undergoing primary knee arthroplasty
Stathellis 2017[272]	Unclear if the study population is people undergoing primary knee arthroplasty
Sugar 2011[274]	Observational study without adjustment for confounding factors
Sundarathiti 2009[275]	Unclear if the study population is people undergoing primary knee arthroplasty
Sundarathiti 2016[276]	Unclear if the study population is people undergoing primary knee arthroplasty
Surdam 2015[277]	Unclear if the study population is people undergoing primary knee arthroplasty
Sveticic 2004[278]	Not review population
Talmo 2018[279]	Incorrect interventions

Study	Exclusion reason
Tan 2001[280]	Unclear if the study population is people undergoing primary knee arthroplasty
Tanikawa 2014[282]	Inappropriate comparison
Tanikawa 2017[281]	Inappropriate comparison
Teng 2012[283]	Observational study without adjustment for confounding factors
Thomas 2014[284]	Observational study without adjustment for confounding factors
Thorsell 2010[285]	Inappropriate comparison
Tierney 1987[286]	Not review population
Toftdahl 2007[287]	Incorrect interventions
Tong 2018[288]	Incorrect interventions
Tontisirin 2017[289]	Unclear if the study population is people undergoing primary knee arthroplasty
Tsukada 2015[290]	Unclear if the study population is people undergoing primary knee arthroplasty
Tugay 2006[291]	Unclear if the study population is people undergoing primary knee arthroplasty
Van beek 2017[295]	Incorrect interventions
Vendittoli 2006[296]	Unclear if the study population is people undergoing primary knee arthroplasty
Vintar 2010[297]	Not review population
Vishwanatha 2017[298]	Unclear if the study population is people undergoing primary knee arthroplasty
Wall 2017[299]	Incorrect interventions
Wang 2002[302]	Unclear if the study population is people undergoing primary knee arthroplasty
Wang 2010[303]	Not in English
Wang 2015[301]	Unclear if the study population is people undergoing primary knee arthroplasty
Wang 2015[304]	Not in English
Weston-simons 2012[306]	Unclear if the study population is people undergoing primary knee arthroplasty
Wiesmann 2016[308]	Inappropriate comparison
Wright 1992[312]	Unclear if the study population is people undergoing primary knee arthroplasty
Wu 2014[313]	Incorrect interventions
Wyatt 2015[314]	Inappropriate comparison
Wylde 2015[315]	Incorrect interventions
Xie 2012[316]	Unclear if the study population is people undergoing primary knee arthroplasty
Yadeau 2013[318]	Inappropriate comparison
Yang 2016[319]	Not in English
Yu 2010[322]	Not in English
Yu 2015[321]	Inappropriate comparison
Yu 2017[323]	Observational study without adjustment for confounding factors
Yu 2018[324]	Unclear if the study population is people undergoing primary knee arthroplasty
Zajonz 2017[325]	Observational study without adjustment for confounding factors
Zaric 2006[326]	Unclear if the study population is people undergoing primary knee

Study	Exclusion reason
	arthroplasty
Zhang 2011[328]	Inappropriate comparison
Zhang 2012[327]	Not in English
Zhu 2017[329]	Not in English
Zinkus 2017[330]	Incorrect interventions

J.21 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 40: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix K: Research recommendations

K.1 Anaesthesia for hip or knee replacement

Research question: What is the clinical and cost effectiveness of adding a nerve block to regional or general anaesthesia, in combination with LIA, for primary elective knee replacements?

Why this is important:

In 2017, there were 108,000 knee replacements performed in the UK, at a cost of over £1Billion to the NHS. These are painful operations, with prolonged recovery times. Better pain relief after surgery is good for patients, may reduce the need for opiates after surgery with their consequent side effects, and may improve rehabilitation and reduce the time spent in hospital. Also, there is some evidence that better pain relief after surgery reduces long term pain after surgery.

One commonly used method for reducing pain after surgery is for the anaesthetist to inject local anaesthetic around some of the nerves that supply the joint, this is called a nerve block. Although the equipment is cheap, performing a nerve block may take up theatre time which can be expensive. There is a small risk of nerve injury, although this is rare. The NICE review was unable to determine whether the addition of a nerve block was clinically effective or cost effective for knee replacement, and could not make a clear recommendation. Local anaesthetic infiltration (LIA) by the surgeon is cheaper, but the use of a block may have benefits over and above that. The relevance of this question to a large number of people, the potential benefit of reducing pain balanced against the potential cost, and the wide variation in practice around the UK, meant that the committee considered this to be a high priority research question.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People undergoing knee replacement surgery Intervention(s): General and/or regional anaethetic, with local anaesthetic infiltration, and the addition of a nerve block Comparison: General and/or regional anaethetic, with local anaesthetic infiltration, and placebo (to be defined by the board or investigators) Outcome(s): 1) Acute pain, determined using a patient reported scale (eg numerical rating scale or visual analogue scale) within the first 24 hours, at day 1,2 and 3 2) Chronic pain, determined using a patient reported scale 12 months after surgery 3) Opiate use 4) Length of hospital stay 5) Health utility (EQ5D) 6) Adverse events 7) Costs and resource use
Importance to patients or the population	Pain is unpleasant, and reduced pain may improve recovery and rehabilitation. Improved pain control may reduce opiate consumption (with consequent side effects such as nausea and drowsiness) and may reduce length of stay. There is also a recognised association between acute and chronic post-surgical pain, but the strength of the association is not known.
Relevance to NICE	The committee were unable to recommend whether or not to use nerve

guidance	blocks for knee replacement. The proposed research would directly influence these guidelines.
Relevance to the NHS	The economic impact of use of nerve blocks is likely to be substantial. Depending on the effect on theatre time and costs of consumables, nerve blocks costing £100-200 per case could have a £20-40M impact on NHS finances overall. These costs might be offset by reductions in length of stay or improved quality of life.
National priorities	This goes towards addressing the James Lind Alliance (Hip and Knee Replacement) Top 10 question: 'What is the best pain control regime pre-operatively, peri-operatively and immediately post-operatively for hip and knee joint replacement surgery for people with osteoarthritis?'
Current evidence base	The review found multiple papers but was not able to determine the clinical or cost effectiveness of nerve blocks when used in addition to LIA, this is the current outstanding clinical question.
Equality	All patient groups suffer with knee arthritis, there is no reason to think that there will be any equality issues. The study will include older and younger people, with a range of disabilities.
Study design	A participant-assessor blinded randomised controlled trial across multiple centres in the UK.
Feasibility	Studies of similar interventions (but different research questions) have been performed previously in the UK and have recruited on time and target (such as APEX, Bristol and PAKA, Warwick), so the study is very likely to be feasible. An internal pilot may be appropriate but a separate feasibility study is not required.
Other comments	
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

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