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[1]
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. .

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

	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 .