Acute Pain Management Incorporating Regional Analgesia in Patients Undergoing Surgery of the Chest, Abdomen, and Pelvis

American Society for Anesthesiologists

Systematic Review Protocol

I. Background

Postoperative pain is often accompanied by physiological and psychological stress responses with short-term and long-term consequences.[1] In addition to patient suffering, inadequate postoperative pain management is associated with persistent postsurgical pain,[2] which can impact long-term quality of life. Postoperative pain is a major concern reported by most surgical patients.[3] Optimal perioperative pain management facilitates postoperative ambulation and rehabilitation. It is thus considered a prerequisite to enhancing recovery after surgery.[1]

Despite concerns for increased postoperative morbidity and mortality from opioid-related adverse events, including persistent postoperative use[4] and opioid use disorder,[5-7] opioids remain the mainstay of perioperative pain management. A retrospective cohort study including 39,140 opioid-naïve patients undergoing surgery found that 3.1% received opioids for more than 90 days following surgery.[6] However, the risk of long-term opioid use varies with the type of surgical procedure.[5-7] Non-surgical risk factors (e.g., anxiety, depression, substance use disorder, socioeconomic status) may also increase the risk of long-term postoperative opioid use.[5-7] Preoperative opioid use is a determinant of long-term postoperative opioid dependence. Goesling et al. followed 574 total knee or total hip arthroplasty patients for 6 months. Of patients taking opioids preoperatively 42% were still using them at 6 months, compared with 9.8% of patients not taking opioids preoperatively.[8]

Suboptimal pain control remains disturbingly high — approximately 75% of surgical patients experience moderate-to-severe pain.[9] Several studies suggest a lack of improvement in pain treatment over the past three decades.[10-12] Although the reasons for the lack of progress in pain management are multifactorial, inadequate clinical application of current knowledge is likely the most important.[1,13,14] Another reason for the lack of improvement may be that existing guidelines[15] provide broad recommendations which may not always apply to specific surgical procedures, making it difficult for clinicians to use the information in day-to-day practice.[16] Also, the confusion among clinicians is probably further increased by conflicting evidence from the systematic reviews assessing various analgesic interventions.[17]

II. Key Questions

1. In patients undergoing elective or urgent surgeries, what are the effectiveness and harms of regional analgesia techniques or select non-pharmacological interventions (i.e., cryoanalgesia) compared with controls (e.g., no intervention, placebo, or sham)?
    a. How do findings vary by patient clinical (e.g., comorbid conditions, type of surgery) or demographic characteristics (e.g., age, sex, race/ethnicity, socioeconomic status).

2. In patients undergoing elective or urgent surgeries, what are the effectiveness and harms of regional analgesia or selective non-pharmacological interventions (i.e., cryoanalgesia and peripheral nerve stimulation [PNS]) alone or in addition to multimodal pain management (including at least 2 out of 3 of acetaminophen, NSAIDs, or other basic analgesia drugs, e.g., dexamethasone) compared with multimodal pain management alone?
    a. How do findings vary by patient clinical (e.g., comorbid conditions, type of surgery) or demographic characteristics (e.g., age, sex, race/ethnicity, socioeconomic status).

3. In patients undergoing elective or urgent surgeries, what are the comparative effectiveness and harms of regional analgesia technique(s) or select non-pharmacological interventions compared with another regional analgesia technique(s)? Example: Peripheral nerve block compared with plane block and/or local infiltration
    a. How do findings vary by patient clinical (e.g., comorbid conditions, type of surgery) or demographic characteristics (e.g., age, sex, race/ethnicity, socioeconomic status).

PICOTS

Population(s)

- Patients of all ages undergoing elective or urgent surgeries with substantive opioid requirements* according to procedure:
    - Intrathoracic (open or minimally invasive)
    - Extrathoracic (mastectomy)
    - Abdominal/pelvic/retroperitoneal (open or minimally invasive)
        - Appendectomy
        - Cholecystectomy
        - Colectomy
        - Colorectal surgery
        - Gastrectomy
        - Hernia repair (inguinal and ventral)
        - Liver resection
        - Hysterectomy
        - Bladder surgery
        - Prostate surgery
        - Nephrectomy
        - Abdominal aortic aneurysm
    - Esophageal surgery
- Subgroups
    - Age
    - Sex
    - Race/ethnicity
    - Socioeconomic status
    - Comorbidities (e.g., ASA physical status or Charlson Comorbidity Index)
    - Psychiatric (e.g., depression/anxiety)
    - Chronic noncancer pain
    - Opioid-naïve
    - Opioid-tolerant
    - History of substance use disorder

Interventions and comparators

Table 1 describes the interventions and potential active comparators (acknowledging the possibility of a multimodal approach of more than one analgesic technique). Relevant comparators include placebo, sham, and control (basic analgesia). Administration of drug includes continuous infusion or single shot.

* Open category for recommended prescribed oxycodone that includes 10 or more 5 mg tablets.

Table 1. Intervention matrix by surgical type.

	Regional Anesthetic Techniques by Surgery							
	Neuraxial Analgesia		Blocks			Wound Infiltration	Non-pharmacologic	
	Epidural	Intrathecal	Paravertebral blocks	Peripheral nerve block	Interfascial plane blocks	Infiltration/ instillation	PNS	Cryoneurolysis/ cryoanalgesia
Intrathoracic	All Procedures	All Procedures	All Procedures			All Procedures	All Procedures	All Procedures
Open				AHRQ	AHRQ			
VATS								
Extrathoracic								
Breast (mastectomy)				✓	✓			
Intrathoracic (esophageas)				✓	✓			
Abdominal/pelvic/retroperitoneal								
Open				✓	✓			
Minimally invasive				✓	✓			

AHRQ: Agency for Healthcare Research and Quality (the shaded section indicates areas where a complementary systematic review is being conducted by the Agency of Healthcare Research and Quality funded by PCORI); PNS: peripheral nerve stimulation; VATS: video-assisted thoracoscopic surgery

Outcomes

Patient-reported

- Postoperative pain intensity
- Postoperative pain trajectory
- Postoperative pain interference
- Quality of recovery
- Health related quality of life (HRQoL)
- Patient satisfaction
- Persistent postsurgical pain (more than 3 months)

Clinical

- Physical functional status
- Immediate postoperative period opioid use (first 72 hours)
- Opioid use through 3 months
- Opioid use beyond 3 months

Harms-intervention specific

- Bleeding
- Epidural hematoma/abscess
- Documented nerve injury
- New onset paresthesia
- New onset motor deficit
- Local anesthetic systemic toxicity (LAST)
- Falls
- Post-dural puncture headache
- Infection

Harms-intervention agnostic

- Delirium incidence
- Complications (cardiac, pulmonary, venous thromboembolic)
- Resource utilization (ICU, blood transfusion)

- Discharge location
- Readmission (due to pain, any)

Timing

- Perioperative period through 1-year

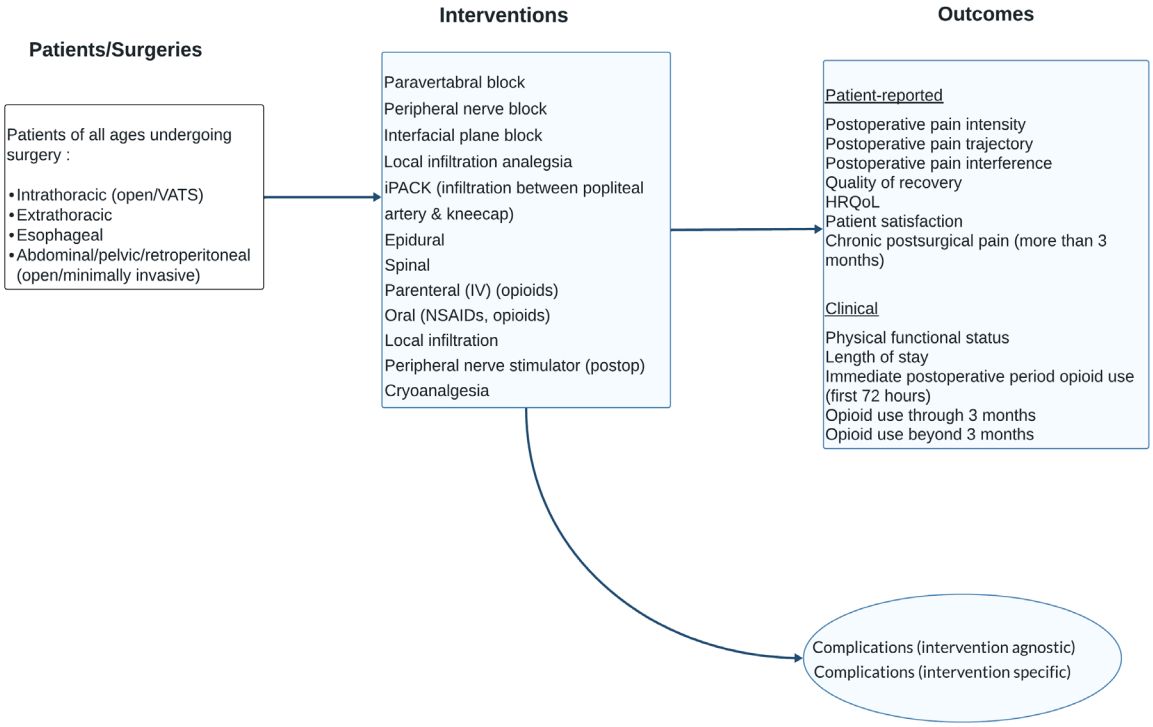
Settings

- Hospital, ambulatory, or other practice setting

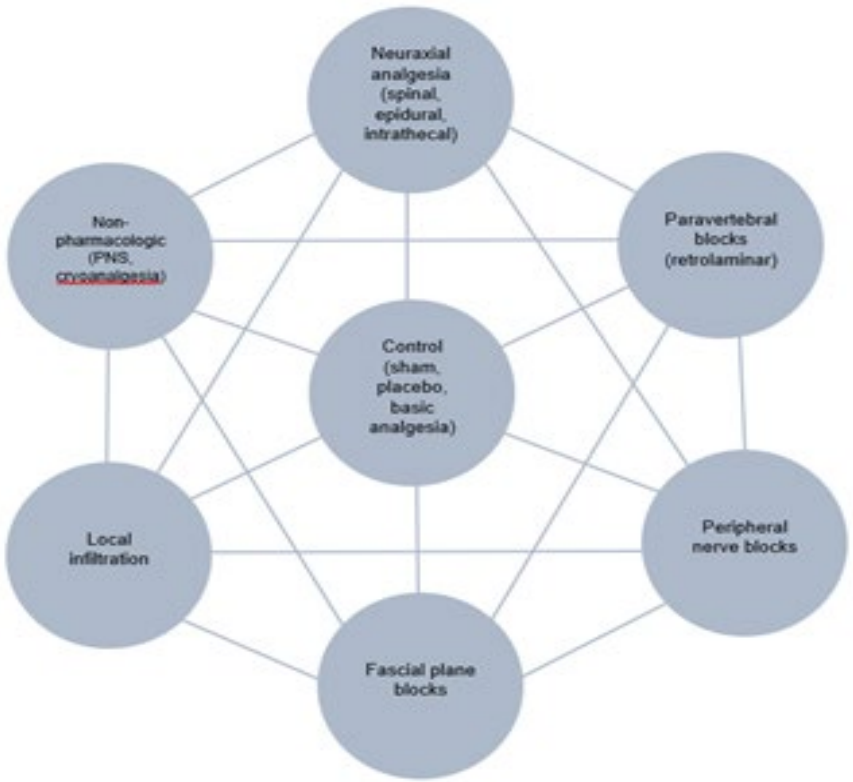
Table 2. Outcome Measures

Outcome	Instruments/measures
Postoperative pain intensity (at rest and motion)	• Numerical Rating Scale (0 = no pain, 10 = pain as bad as you can imagine) • Categorical scale (non, mild, moderate, severe) • Visual analogue scale (VAS) • McGill Pain Questionnaire Visual analogue scale (MPQ-VAS) • Brief Pain Inventory Numerical Rating Scale (BPI-NRS) Pediatric • FACES scale • FLACC
Postoperative pain trajectory	Progression of pain as measured over 0, 6. 12, 24 hours or daily over 1, 2, and 3 days
Pain interference	Example: Daily Sleep Interference Scale (DSIS)
Quality of recovery (QoR)	• QoR-15, QoR-40, and the Postoperative Quality of Recovery Scale
Health related quality of life (HRQoL)	• HOOS quality of life, KOOS quality of life, and WOMAC total score
Patient satisfaction	• American Pain Society (APS) Satisfaction Survey, Patient Outcome Questionnaire **Most studies use Likert scale or dichotomous yes/no
Physical function	• Activities of Daily Living • Brief Pain Inventory (BPI) • Euroqol EQ-5D (EQ-5D) • Oswestry Disability Index (ODI) • Pain Disability Index (PDI) • Roland-Morris Disability Questionnaire (RMDQ) • West Haven-Yale Multidimensional Pain Inventory (WHYMPI) • Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) • 36-Item Short Form Survey (SF-36)
Opioid use (immediate postoperative period 72 hours)	Oral Milligram Morphine equivalent (OME)

Analytic Framework



Evidence Model: Interventions/comparators



Methods

Search

The literature search for the update will include publications from 2013 to the present. Non-pharmacologic intervention literature will be expanded to include studies from 2003 onwards and non-randomized studies.

Criteria for Inclusion/Exclusion of Studies

1. Publication types
   - Published peer-reviewed journal articles or reports
   - Language restrictions: None
   - Limited to humans
2. Study designs
   - Include

     Efficacy or harms
     - Randomized clinical trials (parallel, cluster, crossover)
     - Meta-analyses
   - Exclude
     - Non-RCTs
     - RCTs with fewer than 30 patients per study arm (consideration will be given to smaller studies that assess comparisons not covered by larger studies)
     - Pilot and feasibility trials without sample size calculations
     - Case reports and case series
     - Surveys, questionnaires
     - Letters, editorials, commentary without study findings
     - Conference abstracts or reviews
3. Study topics
   - Exclude studies that compare the following:
     - Dosing
     - Drug vs drug
     - Block technique
     - Opioid efficacy
     - Basic analgesia efficacy
     - Adjuvants
     - General vs regional anesthesia
     - Timing (preop vs. postop)
     - Studies that don't report on at least one critical outcome (postoperative pain or opioid use)

Studies that focus on obstetrical surgeries, head/neck surgeries, or non-spinal neurosurgeries

4. Settings
   - Any practice setting

Search Strategies

Search dates: 2012 – 6/19/2023 (date of search), English language; Searches will be updated prior to finalization of systematic review.

Concept #1: Surgical procedures search terms:

Concept #3: Postoperative outcomes:

"Pain, Postoperative"[Mesh:NoExp] OR "Postoperative Period"[Mesh] OR "Post operat*"[tiab] OR "Postoperat*"[tiab] OR "Post surg*"[tiab] OR "Postsurg*"[tiab] OR "Postoperative Complications"[Mesh] OR "postoperative complication*"[tiab] OR "post operative complication*"[tiab] OR "postsurgical complication*"[tiab] OR "post surgical complication*"[tiab] OR "Quality of Life"[Mesh] OR "quality of life"[tiab] OR "QOL"[tiab] OR "HRQOL"[tiab] OR "Chronic Pain"[Mesh] OR "pain"[tiab] OR "Length of Stay"[Mesh] OR "length of stay"[tiab] OR "Functional Status"[Mesh] OR "functional status"[tiab]

Concept #4: Publication types:

randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical study[pt] OR "randomized controlled trials as topic"[Mesh] OR "Double-Blind Method"[Mesh] OR "randomized controlled trial*"[tiab] OR (randomized[ti] AND controlled[ti] AND trial[ti]) OR "randomized trial*"[tiab] OR "randomised controlled trial*"[tiab] OR (randomised[ti] AND controlled[ti] AND trial[ti]) OR "randomised trial*"[tiab] OR "quasi-experimental"[tiab] OR "double blind"[tiab] OR "clinical stud*"[tiab] OR "placebo controlled trial*"[tiab] OR systematic review[pt] OR "systematic review*"[tiab] OR "review of literature"[ti]

Data Abstraction and Management

Title/abstract and full-text screening, together with data extraction, will be performed on the DistillerSR platform.[18] All screening will be conducted in duplicate, with disagreements resolved by consensus and a third reviewer as necessary.

Anticipated data extraction includes study characteristics (e.g., design, dates, setting, centers, country, funding, registration, subgroups, surgery, and anesthetic), study arm information (e.g., participant characteristics, intervention, and outcomes reported), and outcome detail according to type (e.g., patient-reported, or clinical; continuous, dichotomous, rating scales [Likert, visual analog scale, numeric rating scale]). As required, figures will be digitized. A single reviewer will extract study data followed by verification.[19]

Assessment of Methodological Risk of Bias of Individual Studies

Quality assessment of randomized clinical trials will be conducted using the Cochrane Risk of Bias (RoB) 2.0 tool,[19] for systematic reviews ROBIS will be used,[20] and ROBINS[21] for non-randomized studies. Two reviewers will independently assess the risk of bias for the included studies with discrepancies resolved by discussion and a third reviewer if necessary.

Evidence Synthesis

As appropriate, results will be pooled in pairwise or network meta-analyses based on the number of studies, clinical heterogeneity, and study characteristics. Random effects models are used, given the goal of estimating unconditional effects.[22] Default models will use the Mantel-Haenszel method (an exception being when adjusted effects are pooled) for binomial outcomes and inverse variance weighting for continuous measures. The restricted maximum-likelihood estimator is used to estimate between-study variance.[23] The Hartung-Knapp adjustment will be applied when pooling results from five or more studies.[24] Network meta-analyses will be conducted using frequentist[25] or Bayesian methods[26,27] with non-informative priors. The consistency of network estimates will be examined by comparing direct to indirect evidence[25] for frequentist meta-analyses and inconsistency models[27] in the Bayesian approach. Meta-analyses and network meta-analyses when applicable will be performed in R.[28]

When means and standard deviations are unavailable for continuous or measurement scale outcomes, they will be imputed if authors report medians, interquartile, and/or overall ranges for the effects of interest.[29] If necessary, *P*-values will also be used to estimate missing standard deviations.[30] Relative effects will be pooled as risk ratios for clinical interpretability[31] and continuous outcomes as mean differences or standardized mean differences for measures reported on differing scales. When feasible, standardized mean differences are re-expressed for the most common scale.[32]

Statistical heterogeneity will be examined using the between study variance and I^2.[33] Small-study effects and the potential for publication bias are evaluated in funnel plots (comparison-adjusted for network meta-analyses), by regression-based tests, and with adjustment methods.[28,34] As relevant and practicable, meaningful heterogeneity will be explored in subgroup analysis or meta-regressions.

Grading the Strength of Evidence for Major Comparisons and Outcomes

The overall strength of evidence will be assessed by comparators and outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system of rating evidence from high to very low.[35] Evidence from randomized clinical trials start at high strength of evidence, and nonrandomized studies start at low. The strength will be downgraded based on summary study-level risk of bias, inconsistency, indirectness, imprecision, and other considerations including small study effect due to suspected publication bias (Table 3).

Table 3. GRADE Factors Used to Assess the Quality of a Body of Evidence

Evidence Category	Definition
Study-level risk of bias	Study quality considers the overall risk of bias rating of all the studies included in the evidence base for an outcome.
Inconsistency	Consistency of evidence refers to the degree of similarity in the direction of effects or the degree of similarity in the effect sizes (magnitude of effect) across individual studies within an evidence base.
Indirectness	Direct evidence directly compares interventions of interest in populations of interest and measures patient-oriented outcomes. Evidence can be indirect if the tested intervention differs from the intervention of interest, the study population differs from the population of interest, the outcomes differ from those of primary interest, or treatment comparisons have not been tested in head-to-head comparisons.
Imprecision	Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. Precision is primarily assessed by examining the 95% confidence intervals around the summary effect size.

Date	Section	Modification
03/13/2024	Outcomes	As per task force chairs, no longer considering mortality as it is unlikely that studies will report adequate follow-up for reporting this outcome.
03/24/2024	Scope (PCORI)	ASA and Partners (PCORI, EPC, and AHRQ) came to an agreement for narrowing the scope of work the EPC is covering in their systematic review. EPC will now only cover intrathoracic procedures assessing the effectiveness of PNB and some interfacial blocks for adults only in studies of 60 or more patients in total.
04/03/2024; 05/07/2024	Chair meeting; Task force meeting	2 reviews: one focused on thoracic (trunk); one focused on extremity; exclude studies with fewer than 30 patients/arm, catalog measures of physical function; if studies combine procedures (hip/knee), the study needs to report outcomes separately. If study does not, exclude; include single blinded studies (but do sensitivity analysis). Studies that do not blind patients should be downgraded for blinding on ROB.
04/04/2024	Clinical question	Add definition of usual care as basic analgesia.
05/01/2024	Chair meeting	Multimodal post operative pain management defined as use of 2 or more opioid sparing medications (e.g., NSAIDs, ketamine, gabapentin, etc)

References

1. Joshi GP, Kehlet H: Postoperative pain management in the era of ERAS: An overview. *Best Pract Res Clin Anaesthesiol* 2019; 33:259-67
2. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; 367:1618-25
3. Munafo MR, Stevenson J: Anxiety and surgical recovery. Reinterpreting the literature. *J Psychosom Res* 2001; 51:589-96
5. Jivraj NK, Raghavji F, Bethell J, et al.: Persistent Postoperative Opioid Use: A Systematic Literature Search of Definitions and Population-based Cohort Study. *Anesthesiology* 2020; 132:1528-39
6. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN: Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ* 2014; 348:g1251
7. Stark N, Kerr S, Stevens J: Prevalence and predictors of persistent post-surgical opioid use: a prospective observational cohort study. *Anaesth Intensive Care* 2017; 45:700-6
8. Sun EC, Darnall BD, Baker LC, Mackey S: Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. *JAMA Intern Med* 2016; 176:1286-93
9. Goesling J, Moser SE, Zaidi B, et al.: Trends and predictors of opioid use after total knee and total hip arthroplasty. *Pain* 2016; 157:1259-65
10. Gan TJ: Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res* 2017; 10:2287-98
11. Dolin SJ, Cashman JN, Bland JM: Effectiveness of acute postoperative pain management: I. Evidence from published data. *Br J Anaesth* 2002; 89:409-23
12. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W: Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013; 118:934-44
13. Ladha KS, Patorno E, Huybrechts KF, Liu J, Rathmell JP, Bateman BT: Variations in the Use of Perioperative Multimodal Analgesic Therapy. *Anesthesiology* 2016; 124:837-45
14. Shanthanna H, Ladha KS, Kehlet H, Joshi GP: Perioperative Opioid Administration. *Anesthesiology* 2021; 134:645-59
15. Chou R, Gordon DB, de Leon-Casasola OA, et al.: Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain* 2016; 17:131-57
16. Joshi GP, Kehlet H: Procedure-specific pain management: the road to improve postsurgical pain management? *Anesthesiology* 2013; 118:780-2
17. Kehlet H, Joshi GP: Systematic Reviews and Meta-Analyses of Randomized Controlled Trials on Perioperative Outcomes: An Urgent Need for Critical Reappraisal. *Anesth Analg* 2015; 121:1104-7
18. Partners E: DistillerSR, 2020
19. PCORI: Methodology Standards (11: Standards for Systematic Reviews),
20. Sterne JAC, Savovic J, Page MJ, et al.: RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366:l4898
21. Whiting P, Savović J, Higgins JPT, et al.: ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol* 2016; 69:225-34
22. Sterne JA, Hernan MA, Reeves BC, et al.: ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355:i4919
23. Hedges LV, Vevea JL: Fixed-and random-effects models in meta-analysis. *Psychol Meth* 1998; 3:486
24. Viechtbauer W: Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat* 2005; 30:261-93
25. Cornell JE, Mulrow CD, Localio R, et al.: Random-effects meta-analysis of inconsistent effects: a time for change. *Ann Intern Med* 2014; 160:267-70
26. Rücker GK, U.; König, J.; Efthimiou, O.; Davies, A.; Papakonstantinou, T.; Schwarzer, G.: netmeta: Network meta-analysis using frequentist methods. 2022

27. B'Eliveau A, Boyne DJ, Slater J, Brenner D, Arora P: BUGSnet: an R package to facilitate the conduct and reporting of Bayesian network meta-analyses. *BMC Med Res Methodol* 2019; 19
28. Dias S AA, Welton NJ, Jansen JP, Sutton AJ: Network meta-analysis for decision-making, John Wiley & Sons, 2018
29. Balduzzi S, Rücker G, Schwarzer G: How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019; 22:153-60
30. Shi J, Luo D, Weng H, et al.: Optimally estimating the sample standard deviation from the five-number summary. *Res Synth Methods* 2020; 11:641-54
31. Fu RV, B.W.; Shamliyan, T.A.; O'Neil, M.E.; Yazdi, F.; Fox, S.H.; Morton, S.C.: Handling continuous outcomes in quantitative synthesis. Methods guide for comparative effectiveness reviews, (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I) AHRQ Publication No. 13-EHC103-EF. Edited by Quality AfHRa, 2013
32. Xiao M, Chu H, Cole SR, et al.: Controversy and Debate : Questionable utility of the relative risk in clinical research: Paper 4 :Odds Ratios are far from "portable" - A call to use realistic models for effect variation in meta-analysis. *J Clin Epidemiol* 2022; 142:294-304
33. Higgins JPTT, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. (editors): Cochrane handbook for systematic reviews of interventions version 6.1. *Cochrane* 2020
34. Rücker G, Schwarzer G, Carpenter JR, Schumacher M: Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol* 2008; 8:79
35. Schwarzer G, Carpenter JR, Rücker G: Meta-analysis with R, Springer, 2015
36. Schunemann H, Brozek J, Guyatt G, Oxman A: GRADE Handbook, 2019