**Review title**

Regional anaesthesia for reducing the incidence and severity of chronic pain after surgery: A living systematic review and network meta-analysis. V2

**Original language titl**e: N/A

**Anticipated start date**

May 2024

**Anticipated completion date**

March 2025/ongoing (living systematic review)

**Stage of review at time of submission**

Not started

**Named contact**

Professor Terry Quinn
Professor and Honorary NHS Consultant, University of Glasgow and NHS Greater Glasgow and Clyde
NIHR Evidence Synthesis Group @Complex Reviews Support Unit

**Named contact email**

For this review: Dr Terry Quinn <terry.quinn@glasgow.ac.uk>
For group review activity: Prof Olivia Wu Olivia.Wu@glasgow.ac.uk

**Named contact address (for all group activity):**

Evidence Synthesis Group @CRSU
Clarice Pears Building, University of Glasgow, Glasgow, G12

**Organisational affiliation of the review**

NIHR Evidence Synthesis Group @Complex Reviews Support Unit

**Review team members and their organisational affiliations**

Professor Terry Quinn (University of Glasgow)
Dr Martin Taylor-Rowan (University of Glasgow)
Dr Anna Noel-Storr (Cochrane)
Professor Alex Sutton (University of Leicester)
Professor Olivia Wu (University of Glasgow)
Professor Alan Macfarlane (University of Glasgow)
Dr Brett Doleman (University of Nottingham)
Professor Rachel Kearns (University of Glasgow)
Professor Jonathan Hardman (University of Nottingham)
Professor David Hewson (University of Nottingham).

**Acknowledgement**

This review is being funded by the NIHR Evidence Synthesis Programme.

**Conflict of interest**

The review team members listed above have no relevant conflicts of interest with regard to these materials.

**Collaborators**

We are collaborating with relevant stakeholders who are providing advice on the design, conduct, interpretation and dissemination of the review. These include:

- Local topic experts in fields of anaesthesia (Dr Brett Doleman; Professor Rachel Kearns; Professor Jonathan Hardman; Professor David Hewson; Professor Alan Macfarlane.
- PPI contributors from our ESG PPIE group

**Review question**

Title is framed according to PICOS system.

Full details of each PICOS component below.

**Question:** Does the use of regional anaesthesia at the time of surgery reduce the incidence and severity of chronic postsurgical pain (CPSP) and/or long-term opioid consumption?

**Population:** Adult and paediatric patients undergoing surgical procedures where chronic postsurgical pain is common (these have been defined as: open laparotomy, laparoscopic abdomino-pelvic surgery, major lower limb amputation, caesarean section, laparoscopic cholecystectomy, knee arthroplasty, hip arthroplasty, open inguinal hernia, mastectomy, sternotomy, Video Assisted Thoracoscopy (VATs), open thoracotomy, and craniotomy).[1]

**Intervention (model):** Any regional anaesthetic technique where nerves are targeted with local anaesthetic including: neuraxial techniques, peripheral nerve blocks, and peripheral nerve catheters.

**Comparator:** Any sham technique with placebo solution or no regional blockade (such as use of general anaesthesia only), or other intervention arms meeting the inclusion criteria above.

**Primary outcome:** Incidence of CPSP (at any time point ≥ 3 months after surgery, categorised as time points). This will be examined for all surgeries combined, then if data allow by specific surgery and anaesthesia type.

**Study type:** Randomised controlled trials.

**Secondary outcomes:**

- Incidence of CPSP at 3-<6 months, 6-<12 months inclusive, 12-<24 months inclusive, ≥24 months
- Incidence and/or amount of opioid consumption 3-<6 months, 6-<12 months inclusive, 12-<24 months inclusive, ≥24 months
- Serious adverse events both short and longer term (such as local anaesthetic toxicity, rebound pain)

**Searches:**

The following databases will be searched:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- Embase (Ovid SP)
- MEDLINE (Ovid SP)
- ClinicalTrials.gov
- WHO trials portal: ICTRP

Searches will be restricted by:

- We will exclude animal and pre-clinical studies.
- Search will be limited to English language in the first instance.
- Search will be limited to studies published in peer reviewed scientific journals (i.e. there will be no searching of pre-print servers or other grey literature).
- We will search from 2000, recognising the major changes in surgical technique in last decades.
- Searches will be updated 4-monthly upon completion of the baseline review to ensure the review remains up to date with new evidence.

**Other searches:**

We will check the reference lists of all potentially includable studies and relevant reviews for any additional potential studies.

The full search strategies for MEDLINE database will be published in the final review.

Search methods will be reviewed annually to ensure they remain adequate for capturing the evolving literature.

**Results screening:**

We will use Cochrane's crowdsourcing service Screen4Me to remove off-topic material.[2] We will supplement this with the PICS relevance classifier to further reduce off-topic material.[3] Once complete the core author team will assess the remaining results. Details of this process can be seen in the 'Data extraction' section below.

**Condition or domain being studied**

This review will consider post-surgical pain. Under the term 'surgical' we will include emergency and elective procedures and obstetric procedures in our initial searches. We have defined a list of surgeries associated with chronic pain (see above) and these will be the focus of the review.

**Participants/population**

Participants will be limited to adult surgical (age over 16 years) and paediatric (age 1 year to 16 years) populations. We will treat these populations as distinct.

All surgical procedures previously described will be considered including emergency and elective. Obstetric procedures will be included.

**Interventions/exposures**

The focus of the review will be on the effects of regional anaesthesia on chronic pain. Regional anaesthesia involves the direct application of local anaesthetic to the nerves which has the potential to completely abolish pain during the postoperative period. Therefore, it represents a promising intervention in reducing the incidence of post-surgical pain. This may in turn reduce more chronic pain related complications.[4]

Numerous approaches to regional anaesthetic exist; hence, we will also use a network approach to evaluate the comparative effectiveness of these interventions to identify the best approaches to regional anaesthetic.

**Comparator/control**

The benefits of regional anaesthesia will be compared against placebo and no regional block (e.g. general anaesthetic).

**Types of study to be included**

We will include randomised controlled trials that examine the effect of regional anaesthesia on chronic pain.

Reviews will not be included, but their reference lists will be hand searched for relevant titles.

**Context**

The degree of activation produced by a surgical incision and the response from surrounding immune,

stromal and glial cells, influences the extent and duration of pain as well as its transition to chronic pain. Regional anaesthesia given in the acute period may therefore prevent transition to CPSP by modulating pain signalling created by a surgical incision.[4]

Management of chronic pain ranks highly in recent James Lind Alliance PSP's. A UK patient and clinician priority setting exercise identified whether regional anaesthesia reduced chronic post-surgical pain as one of the top ten research priorities. Regional anaesthesia is associated with reduced instances of chronic pain.[5] However, specific questions around the use of regional

anaesthesia to prevent chronic pain remain to be answered, including use of individual regional techniques and whether there is variability in specific patient groups or surgical procedures.

Reductions in chronic opioid addiction and post-surgical pain has implications for patients undergoing surgery, the NHS and wider society. For the NHS, it can directly reduce the costs of medications and chronic pain interventions and reduces healthcare utilisation. Social care is benefitted as opioid addiction can lead to family breakdown and loss of custody of children from opioid misuse.

**Outcomes**

The primary outcome will be pain at ≥ 3 months after surgery. We will assess pain at other time points post three months.

We will accept any recognised measure of pain including validated pain questionnaires. Where the outcome is measured but not reported in the main text, we will contact study authors.

We will extract odds ratios for binary outcomes. Where standard means differences are reported for continuous outcomes, we will convert these to odds ratios (or vice versa depending on what is more common) using guidance set out in the Cochrane handbook.

**Additional outcomes**

Secondary outcomes will be:

Chronic pain at certain time points (6-<12 months, 12-<18 months, ≥18 months)

Opioid consumption at 3-<6 months, 6-<12 months, 12-<18 months, ≥18 months (measured dichotomously i.e. on opioids Y/N)

Adverse effects, both early and late, including rebound pain will be assessed, (while rebound will not be an issue in comparator arms not receiving regional anaesthesia, these data will be useful for network comparative analyses of differing regional anaesthesia approaches).

**Data extraction**

All references identified by the searches and from other sources will be uploaded into reference management software and de-duplicated. Minimum 20% of the titles and abstracts will be reviewed by two reviewers for eligibility, with any disagreements resolved by discussion or, if necessary, a third independent reviewer will have the final say. Where there is more that 20% disagreement on included studies, all abstracts will be reviewed by a second reviewer.

The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.

A standardised form will be used to extract data from studies. Data extraction will be performed by one reviewer and cross checked by a second reviewer.

To avoid duplication of effort, where possible, we will try to obtain data extracted from previous Cochrane reviews from relevant trials. Researchers who share extracted data from previously published reviews will be offered authorship on the review.

We hope that the review could contribute to a cross-ESG study within a review (SWAR) looking at new genAI for data extraction. Details of the SWAR, if agreed, will be given in a separate protocol.

Data to be extracted will include (based on scoping, engagement with clinicians and Cochrane RCT template):

- Study specific: year of paper, study dates, country, number of centres.
- Surgery details: surgery classification (acute/elective), surgical procedure (open/laparoscopic), surgical site (anatomical), operation(s).
- Baseline features: age, sex (% female), ethnicity, number randomised per group, % missing data, other relevant sociodemographic info, pre-surgery analgesia usage, baseline pain scores.
- Methods: original dataset details (method of randomisation, blinding etc), these will inform Risk of Bias assessments.
- Intervention: anaesthesia method, duration of intervention, timing of intervention (pre-post incision).
- Comparator: specific intervention, duration of intervention, timing of intervention (pre-post incision)
- Outcomes: chronic pain measurement tool employed, timing of measurement, mean and SD of pain outcome in intervention/control groups.

Study investigators may be contacted for missing data where time and resources allow.

**Risk of bias assessment**

Risk of bias will be assessed using the Cochrane ROB1 tool. Risk of bias assessment will be performed by two reviewers working independently and comparing results with final decision based on consensus and discussion with the broader team.

RoB1 involves assessment of the following 6 domains to cover key aspects of RCTs: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

On the basis of the ROB classifications for each domain, assessors will judge the overall ROB of the trial as low, high, or unclear. We will present risk of bias at study level and aggregate, using a 'traffic light' style data visualisation. If data allow, we will perform a sensitivity analysis restricted to studies at low risk of bias.

**Strategy for data synthesis**

In the first instance data will be presented using a mix of data visualisation, tabulation and narrative description to outline similarities and differences between respective trials.

In the initial quantitative analyses, we will compare regional anaesthesia versus comparator. Analyses will consider all trials in aggregate with variables entered in a meta-regression.

Then, as data allow, analyses be repeated for individual surgeries and then for individual anaesthesia approaches. Network meta-analysis (NMA) will then be performed, if data allow, comparing anaesthesia intervention approaches.

To complement the aggregate meta-regression, we will perform a series of secondary outcome sensitivity and subgroup analyses to investigate variability on CSPS outcomes at different time points, relationship with opioid consumption, and adverse events (including rebound pain) using the same approach (i.e. all surgeries included then each analysis for each distinct subgroup). We anticipate baseline risk (i.e. the level or percentage of those who have pain in the study population) will be a significant effect modifier for pain score data. If this is the case, then estimates will be reported from a fixed value of this covariate.

We will consider NMA as appropriate when the identified studies are considered sufficiently robust and comparable, and where there are data from more than three independent datasets to include. The NMA will produce a summary result with its corresponding 95% confidence intervals. A random effects approach will be used to allow for unexplained heterogeneity across studies. We will examine potential small study effects within NMA. Specific tests used to assess for small study effects will depend upon whether there are continuous outcomes included and on the direction of bias in respective comparisons.

**Assessing heterogeneity:** We expect heterogeneity in relation to factors such as the population age, year of surgery and acuity of the surgery. We plan subgroup analyses to explore both these and other relevant (previously described) factors. Heterogeneity across all the RCT's may be seen by surgical procedure and we will assess this using prediction intervals. It is hoped the use of network meta-regression[6] will address any factors causing inconsistency in the network analyses, however a full inconsistency assessment will be carried out after including such covariates, where possible, to explore whether residual inconsistency remains. The Deviance Information Criteria (DIC) will be used to help guide selection of covariates with the aim of producing final models.

**Certainty of estimates:** We will use the Confidence in Network Meta-Analysis (CINeMA) approach to rate the confidence in our summary of each treatment effect.[7] Within this framework we will consider within-study bias (from ROB assessment), reporting bias (from tests for small study effects), indirectness, imprecision, heterogeneity, and incoherence. We will present these data using the Cochrane Summary of Findings table format.

**Updating evidence:** We will repeat the prespecified analysis for all review updates, where appropriate, based upon the availability of new data. For all updates, a decision framework will be followed to determine whether any new trials will be incorporated into a new review. Specifically, decisions will be based on whether new trials are likely to impact the conclusions of the review. To determine this, a preliminary analysis incorporating new trials will be run. The review will be updated if incorporation of the new trials leads to a change in the CINeMA rating; introduces evidence pertaining to new populations, serious adverse events, or other clinically meaningful findings as judged by the author team.

**Analysis of subgroups or subsets**

If data allow, we plan the following subgroup and sensitivity analyses:

- Differing surgery groups will be assessed individually if data allow.
- Differing block types will be assessed individually if data allow.
- Adult and paediatric populations will be assessed separately.
- Risk of bias (restricted to studies at low risk of bias)
- Surgery acuity (emergency versus elective)

Specific subgroups of interest:

- Neuraxial vs peripheral nerve block vs no nerve block
- Single administration anaesthetic versus continuous infusion

Covariates of interest:

- Patients with pre-existing chronic pain or opioid use vs those without

- Use of other analgesic agents
- Females vs males
- Other risk factors for CPSP if available (e.g. BMI, pre-existing anxiety disorder)

**Type and method of review**

Intervention review with potential for network and living review aspects

**Language**

English

**Other registration details**

Nil

**Reference and or URL for published protocol**

TBC

**Dissemination plans**

We will use a range of different methods to raise awareness. These include standard approaches such as:

- notifying registered stakeholders of publication
- issuing a press release or briefing as appropriate.

Our dissemination will benefit from the early and ongoing involvement of a group of clinical experts in the field who have leadership positions in regional anaesthesia special interest groups and professional societies.

Alongside the above dissemination plans, we would plan to publish the review in a peer reviewed scientific journal. Our topic experts in anaesthesia will advise, once the review is complete, whether there is potential to present the results at a discipline specific meeting. If presenting these data, we will encourage our early career team member to take a lead on this aspect.

In addition, regular updates to the living systematic review will be published on our evidence synthesis website. Substantial updates to the review will be published in a peer-reviewed journal or online, as required.

**Keywords**

Randomised controlled trial, anaesthesia, surgery, pain

**Details of any existing review of the same topic by the same authors**

Nil

**Current review status**

Ongoing

**Any additional info**

Involvement of stakeholders: We will work with our PCPI lead and other team members to develop a strategy around involving stakeholders. We anticipate that we will include potential 'end users' of our review findings i.e. anaesthesia experts, and potential beneficiaries of any change to policy i.e. those with experience of post-surgical pain.

An evaluation of the need to maintain the living systematic review will be carried out annually. The review will be transferred out of living mode once the certainty of evidence is judged to be high for all prespecified outcomes, if the research question is no longer a priority for decision-making, or if the research area is no longer active.

**References:**


1. Rosenberger DC, Pogatzki-Zahn EM. Chronic post-surgical pain - update on incidence, risk factors and preventive treatment options. BJA Educ. 2022 May;22(5):190-196. doi: 10.1016/j.bjae.2021.11.008. Epub 2022 Feb 24. PMID: 35496645; PMCID: PMC9039436.
2. Noel-Storr A, Dooley G, Affengruber L, Gartlehner G. Citation screening using crowdsourcing and machine learning produced accurate results: Evaluation of Cochrane's modified Screen4Me service. J Clin Epidemiol. 2021 Feb;130:23-31. doi: 10.1016/j.jclinepi.2020.09.024. Epub 2020 Sep 30. PMID: 33007457.
3. Thomas J, McDonald S, Noel-Storr A, Shemilt I, Elliott J, Mavergames C, Marshall IJ. Machine learning reduced workload with minimal risk of missing studies: development and evaluation of a randomized controlled trial classifier for Cochrane Reviews. J Clin Epidemiol. 2021 May;133:140-151. doi: 10.1016/j.jclinepi.2020.11.003. Epub 2020 Nov 7. PMID: 33171275; PMCID: PMC8168828.
4. Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. Br J Anaesth. 2013 Nov;111(5):711-20. doi: 10.1093/bja/aet213. Epub 2013 Jun 28. PMID: 23811426; PMCID: PMC3793661.
5. Ferry J, Lewis O, Lloyd J, et al. Research priorities in regional anaesthesia: an international Delphi study. Br J Anaesth. 2024 May;132(5):1041-1048. doi: 10.1016/j.bja.2024.01.033. Epub 2024 Mar 5. PMID: 38448274; PMCID: PMC11103078.
6. Cooper N, Sutton A, Morris D, Ades A, Welton N. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Stat Med*. 2009;28:1861-1881
7. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. (2020) CINeMA: An approach for assessing confidence in the results of a network meta-analysis. PLoS Med 17(4): e1003082. https://doi.org/10.1371/journal.pmed.1003082