# Performing a systematic review and/or meta-analysis of studies reporting results for acute postoperative pain in adults: a quick check of some critical elements for pain reporting and analysis

The evaluation of analgesic effects in acute pain situations has been studied intensively for over 75 years. Many of the elements of clinical trials that we now consider to be essential were routine in pain trials 60 years ago. Subsequent research, especially analysis at the level of the individual patient, has confirmed and reconfirmed those early findings, and has added more possibilities for misleading results.

* This checklist is aimed at helping those performing systematic reviews in adults (especially Cochrane Reviews) to avoid known pitfalls for acute pain.
* Each point is based firmly on evidence from pain analyses.
* There will be many circumstances where pain is a secondary outcome and studies may not fulfil some or all of these criteria: but as far as possible these criteria should be used for evaluation of **pain outcomes**.
* The presence or absence of checklist points should help in making a GRADE assessment about pain outcomes.
* The checklist supplements guidance in the Cochrane Handbook around risk of bias (Higgins 2021), but uses wording from the Oxford Quality Score to exclude studies that are inadequately randomised or double blind as these are key issues in the subjective measure of pain (Control Clin Trials. 1996;17:1-12).

Note that the checklist is accompanied by sets of slides, short online lectures, and reference lists that fill out:

* some background to postoperative pain and its importance ([slideset 1: Intro to postop pain](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/1_papas_nif_intro_to_postop_pain_mar21.pptx));
* measurement of pain emphasising the importance of patient reporting ([slideset 2: Measuring postop pain](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/2_papas_nif_measuring_postop_pain_mar21.pptx));
* outcomes in pain trials emphasising patient-reported outcomes of value to people with pain ([slideset 3: Outcomes](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/3_papas_nif_outcomes_mar21_0.pptx));
* fundamental considerations in acute pain studies ([slideset 4: Fundamentals](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/4_papas_nif_fundamentals_mar21.pptx));
* issues of interpretation of evidence around small studies, and small numbers of small studies in postoperative pain ([slideset 5: Study size](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/5_papas_nif_study_size_mar21.pptx));
* an examination of dealing with publication bias used in acute pain studies ([slideset 6: Publication bias](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/6_papas_nif_publication_bias_mar21.pptx));
* a worked example of possible sensitivity analyses that can be used in postoperative pain ([slideset 7: Lessons in practice](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/7_papas_nif_lessons_in_practice_mar21.pptx)).

## **The Checklist**

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|  | Clinical trial description | Consider | Reason |
|  | Design elements known to have major effects on efficacy estimates: inadequately designed trials should **usually** be excluded | | |
| 1 | Is the trial properly randomised?  A validated way of looking at this is given below. | Exclude any trial that is not properly randomised – including quasi randomised, or randomised using inadequate methods.  While randomisation is captured by risk of bias (RoB), pain outcomes are particularly sensitive to bias where trials are not properly randomised and allocation concealed. This should inform your interpretation of the results and contribute to your GRADE rating of the outcome. | For pain, inadequately randomised trials can grossly overestimate efficacy estimates, and can give completely different results from properly randomised trials.  A sensitivity analysis is strongly recommended for properly randomised and concealed trials. |
|  | **Randomisation**: If the word randomised or any other related words such as random, randomly, or randomisation are used in the report, but the method of randomisation is not described, give a positive score to this item. A randomisation method will be regarded as appropriate if it allowed each patient to have the same chance of receiving each treatment and the investigators could not predict which treatment was next. Therefore methods of allocation using date of birth, date of admission, hospital numbers or alternation should not be regarded as appropriate.  ***Link to*** [***Slideset 4: Fundamentals***](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/4_papas_nif_fundamentals_mar21.pptx) | | |
| 2 | Is the trial properly double-blind?  A validated way of looking at this is given below. | Exclude any trial that is not properly double-blind.  While blinding is captured by RoB, pain outcomes are particularly sensitive to bias where trials are not properly randomised and allocation concealed. This should inform your interpretation of the results and contribute to your GRADE rating of the outcome. | For pain, inadequate blinding can grossly overestimate efficacy estimates, and can give completely different results from properly double-blind trials.  A sensitivity analysis is strongly recommended for properly blinded trials. |
|  | **Wording on double-blinding**: A study must be regarded as double-blind if the word double-blind is used (even without description of the method) or if it is implied that neither the caregiver nor the patient could identify the treatment being assessed.  ***Link to*** [***Slideset 4: Fundamentals***](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/4_papas_nif_fundamentals_mar21.pptx) | | |
|  | Note that there are a number of non-pharmaceutical interventions where adequate blinding of participant and observer is at best difficult, and often impossible. In this circumstance trials should be included, and risk of bias assessed using the Cochrane Risk of bias 2 tool. | | |
| 3 | Does the trial specify that pain measurement is made by the participant rather than someone else? | Exclude any trial where pain measurements are made by observers. Pain measurement made by the participant is essential in all circumstances where participants are able to do this or can communicate.  Pain measures not made by participants should inform your interpretation of the results and contribute to your GRADE rating of the outcome. | Pain measurements by someone other than the person with pain is associated with very considerable underestimation of pain, and the underestimation is greater the more severe the pain. |
|  | Note that this applies only to adults who are able to communicate. This cannot apply adults are unable to communicate, and to some circumstances for children. Pain measurement in those circumstances is guided by different considerations  ***Link to*** [***Slideset 2: Measuring postop pain***](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/2_papas_nif_measuring_postop_pain_mar21.pptx) | | |
| 4 | Does the trial specify that initial pain before treatment is moderate or severe? | ***In trials of treatment of established acute pain***, the pain level should be at least moderate (usually 4/10 on numeric rating scale (NRS), or 40/100 on visual analogue scale (VAS)) to ensure sensitivity.  ***In studies to prevent pain occurring***, pain levels in control groups should be significant (usually above 3/10 on NRS, or 30/100 on VAS).  Inadequate baseline or comparator pain should inform your interpretation of the results and contribute to your GRADE rating of the outcome. | Where initial pain is not at least moderate in intensity there is lack of sensitivity, and analgesic effects can be underestimated.  There are good reasons to consider excluding studies with low initial pain intensity as their results can be misleading, but if they are included a sensitivity analysis is strongly recommended. |
|  | Note that initial pain intensity, or adequate pain with control represent design elements that are known to have important effects on efficacy in some circumstances.  ***Link to slidesets*** [***2: Measuring postop pain***](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/2_papas_nif_measuring_postop_pain_mar21.pptx) ***and*** [***7: Lessons in practice***](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/7_papas_nif_lessons_in_practice_mar21.pptx) | | |
|  | Design elements known to have major effects on efficacy estimates: inadequately designed trials should **usually** be excluded | | |
| 5 | Is the pain condition studied defined with standard diagnostic criteria or is pain associated with a particular situation? | Check for consistency across trials and comment in results if there are inconsistencies. | Response of pain to analgesic interventions can vary according to the pain condition studied: both effects observed with intervention and effects observed with placebo can vary. |
| 6 | Check how the trial deals with withdrawals or dropouts (or remedication) in data analysis. | Check the paper for how this is dealt with.  Three methods are typically used: reporting completers only, using last-observation-carried-forward (LOCF), or using baseline-observation-carried-forward (BOCF).  Similar information will normally be captured in the incomplete outcome data (attrition bias) risk of bias domain (RoB1) or the bias due to missing outcome data (RoB2). The importance of imputation for pain outcomes should inform your interpretation of the results and contribute to your GRADE rating of the outcome. | BOCF is the most conservative of these three methods. LOCF is known to overestimate treatment effects where observations extend beyond 6 hours, and a completers analysis usually means the analysis is not intention to treat (ITT).  A sensitivity analysis is strongly recommended where different imputation methods have been used. |
|  | ***Link to*** [***Slideset 4: Fundamentals***](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/4_papas_nif_fundamentals_mar21.pptx) | | |
|  | Outcomes used in acute pain: pitfalls and problems | | |
|  | ***Link to*** [***Slideset 3: Outcomes***](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/3_papas_nif_outcomes_mar21_0.pptx) |  |  |
| 7 | Analysis of average pain results – pain scores or change in pain. | Be cautious about interpretation of averages for pain scores.  When pain scores are normally distributed, it is fine to compare average scores. However, if pain scores cannot be shown to be normally distributed, it may be inappropriate to compare average pain scores.  The type of outcome reported (average values or responder analyses) may influence your interpretation of the results and contribute to your GRADE rating of the outcome. | Mean pain scores are known to be misleading for pain, describing the experience of few participants.  Responder analyses are preferable and typically bimodal – good/very good or poor/very poor. Because distribution is not Gaussian, averages can be misleading. |
| 8 | Can you abstract numbers of persons responding at ≥ 50% pain intensity reduction or ≥ 50% pain relief, or those with no worse than mild pain? | Choose these outcomes if available or calculable. These are ideal outcomes in pain. | Multiple reasons, including:   * it is an outcome of importance to people with pain; * it fairly describes the experience of people with pain; * it sensitively discriminates between analgesic interventions of different efficacy. |
| 9 | Can you abstract measures relating to the duration of analgesia – for example how long before additional analgesia is given, or the percentage of participants remedicating by a particular time? | Look for this outcome and report in your results; it may be described in a variety of ways. This is an outcome that has been described as very useful by nursing staff. | This outcome has practical impact for persons with acute pain in hospital, especially postoperatively. Obtaining additional analgesic prescription can be delayed, and is a major cause of distress to people with pain. |
| 10 | Can you abstract measures relating to analgesic consumption (opioid consumption in many postoperative studies)? | Reduced postoperative analgesic consumption resulting from a perioperative intervention may be desirable (low consumption is related to better patient attitudes to analgesia).  But be cautious about interpretation. | This outcome is often used, but analgesic consumption postoperatively has a highly skewed distribution, and mean, median, and mode are quite different from one another.  Differences of a few mg in mean opioid consumption may be statistically significant, but of no clinical value. |
| 11 | Significant adverse events, most often postoperative nausea and vomiting (PONV). | Look for this outcome and report in your results. Consider the information of how adverse events were measured and categorised/classified within the trial. | PONV can be distressing and time consuming. There are various definitions of nausea, vomiting, or any emetic event, and interpretation can be complicated due in part to widely different incidence of PONV in apparently similar studies. |
| 12 | Duration of hospital stay. | Be cautious about accepting reported results, though this can be a very important outcome. | The duration of hospital stay can be influenced by many different events unrelated to perioperative or postoperative events (such as delay in obtaining take-home drugs). Few studies give sufficient detail to be certain about the robustness of this outcome. |
|  | Additional important issues for sensitivity analysis or for considering during GRADE assessment | | |
| 13 | Studies are small (small < 50 per treatment arm; intermediate 50-199 per treatment arm; large ≥ 200 per treatment arm). | Explore the data for evidence of small study effects and perform sensitivity analysis for smaller studies against larger studies.  The size of available studies and results of sensitivity analyses should inform your interpretation of the results and contribute to your GRADE rating of the outcome. | There is considerable evidence that small studies can overestimate treatment effects, especially in pain.  There are good reasons to consider excluding small studies as their results can be misleading, but if they are included a sensitivity analysis is strongly recommended. |
|  | ***Link to Slidesets*** [***5: Study size***](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/5_papas_nif_study_size_mar21.pptx) ***and*** [***7: Lessons in practice***](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/7_papas_nif_lessons_in_practice_mar21.pptx) | | |
| 14 | Is there susceptibility to publication bias? | Especially if a review contains small numbers of small studies and there are dichotomous outcomes reported and analysed, then a calculation of the susceptibility of any result to publication bias should be done. | Susceptibility to publication bias is high with small numbers of small studies and minimal clinical effectiveness – small numbers of participants in trials with no benefit would be needed to overturn any result. Susceptibility to publication bias is low with large studies and significant clinical effectiveness – large numbers of participants in trials with no benefit would be needed to overturn any result.  Establishing susceptibility to publication bias can be critical when making a GRADE assessment. |
|  | ***Link to*** [***Slideset 6: Publication bias***](https://papas.cochrane.org/sites/papas.cochrane.org/files/public/uploads/6_papas_nif_publication_bias_mar21.pptx) | | |

## Reference

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).

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