Author’s response to reviews

Title: Risk Factors for Addiction Among Patients Receiving Prescribed Opioids: A Systematic Review Protocol

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Author’s response to reviews:

Reviewer #1:

1. How did you decide on excluding studies with 50% patients who fall in your exclusion criteria?

Risk factors for opioid addiction among patients whose first opioid exposure is through prescribed opioids are likely to vary substantially from patients first exposed to illicit opioids. If we were to include many patients who were first exposed to illicit opioids, their risk factors would be included in the development of primary prevention strategies we are hoping to develop, which may render these strategies ineffective, as they would target the wrong risk factors. As a result, we defined our inclusion/exclusion criteria to be broad enough to capture studies who enrol mixed populations to ensure we do not miss relevant information, while limiting our analysis to either include patient-level data from patients exposed through prescribed means from mixed studies (when available), or, if we are unable to obtain patient-level data, to studies who enrol more than half of patients who were first exposed to opioids using the route of interest.

In the Methods section we have explained that we will seek patient-level data first, for any mixed studies, and only if patient-level data cannot be obtained, exclude studies for which over 50% of patients do not meet our inclusion criteria. We will subsequently conduct sensitivity analyses to understand the effect of including studies with mixed populations on our results. Please note that we are unaware of any methodological literature that could guide the percent choice of patients.
who meet/don’t meet the inclusion and exclusion criteria, and therefore the 50% cut-off is
arbitrary (We have made a minor edit to clarify this, see Methods, Population, p 6-7.)

Reviewer #2:

2. Opioid epidemics are a very hot topic in North America. The potential implication of this
review, which is "reducing opioid prescribing among opioid-naïve patients at high-risk of
developing subsequent addiction", is very interesting and valuable. I can't wait to read the
review conclusion.

With that said, however, this protocol has three major areas for improvement. The first area for
improvement is the lack of discussion on potential risk factors. There is only one sentence under
the subheading "Topic" in this regard. It is not enough to just take a figure from another paper
without even minimum discussion on its applicability to your review. If I understand correctly,
the figure is just for patient-level risk factors. Then the protocol presents no discussion on
provider- and system-level risk factors. It is important to have some discussion on potential risk
factors because of two reasons. Firstly, it could help/accelerate the search and screening of
articles (and help other researchers to replicate your search and screening). Secondly but most
importantly, in order to fulfill your objective to reduce opioid prescribing among opioid-naïve
patients at high-risk of developing subsequent addiction, these risk factors have to be observable
by providers at the point of prescribing. I can't stress this more as I don't want to you to waste
time on finding evidence for some risk factors that can't immediately inform change in practice
because they are not easily observable for prescribers at the point of care. Some hypothetical
examples would be a fancy genetic testing that is not universally available, or a sensitive
personal matter that is not usually shared during a clinical encounter. So I would suggest you to
define the scope of risk factors, and only collect evidence for those that are measurable at point
of prescribing.

In our previous experience in developing clinical decision rules to help clinicians risk stratify
patients for clinical conditions, system and provider-level risk factors were useful.1 An example
of observable and modifiable system-level variables that may be relevant in this work is the
provision of narcotics “to go”. In our emergency department, we can dispense bottles containing
6 tablets of a narcotic analgesic to patients who would otherwise have difficulties or be unable to
fill a prescription (e.g., night time, destitute). This is a modifiable system-level factor that could
be removed, should it be related to promoting addiction. Similarly, patient education about the
risks of subsequent addiction, the intensity of nurse-initiated non-narcotic could have an impact
on downstream narcotic prescription, and addiction risk.

A recently published NEJM manuscript revealed an important modifiable provider-level
variable, the provider’s intensity of narcotic prescribing.2 Patients treated by high-intensity
narcotic prescribers were more likely to become addicted to narcotics than those treated by low-
intensity narcotic prescribers. This is something that could be addressed through education. Other provider-level factors that may be relevant include the type of narcotic prescribed (often a provider is more likely to prescribe one or two types of medications).

We agree that our focus should be on modifiable and observable risk factors and edited to our objective statement (p. 5) and the methods (Topic, p.8) to reflect this important point.

3. The second area for improvement is the inconsistency in different parts of the protocol. For example, "drug-/"medication-" level risk factors are mentioned in some places but not in others. Another example is that in Abstract's Method session, it says you "will perform subgroup analyses for naïve patients". This is not consistent with the title and the Population session in the full text, where opioid-naïve patients are the only/main group for analysis instead of a subgroup. One more example is that in the Objective session, it mentions to synthesize evidence on "prescription (e.g., type of drug, dosage, quantity dispensed, length of exposure) of the initial opioid prescription", which is not in Appendix C Data Collection Form.

Thank you for pointing this out. We have reviewed the title, protocol and data collection forms, and addressed inconsistencies.

While we plan to focus on opioid-naïve patients as the main population of interest, we will not exclude studies that include non-opioid-naïve patients as we would likely loose valuable information. Instead we plan on conducting our analysis on opioid-naïve patients using a sensitivity analysis. We decided on this approach for two reasons: Studies may not have screened for opioid-naïve status, and therefore, we risk excluding studies with valuable information if we used opioid-naïve status as an exclusion criterion. Inclusion of both study types will allow us to make comparisons between these populations.

4. The third area for improvement is that there is not enough discussion on how to handle evidence from different study designs. Special caution should be taken when a review is looking at both randomized and non-randomized studies. More discussion is needed on topics like whether data from randomized and non-randomized studies will be analyzed together or separately; what if data from different study types differ significantly; how to handle adjustment and confounders in observation studies, etc. Now the only discussion in this regard is the different tools for Risk of Bias assessment.

Thank you for pointing out this omission. Data from studies of different designs will be analysed separately, as the biases inherent in and effect size estimates derived from different study designs commonly vary.3 We have clarified this in the Methods section (Data Synthesis, p.12) Differing
or opposing pooled effect size estimates derived from different study designs will be discussed qualitatively.

Reviewer #3:

This is a well-written protocol on an important topic, and I strongly recommend it for publication. There are, however, a number of issues which should be addressed beforehand:

5. Page 2, line 2-4: "In 2016, opioid addiction prevention became an urgent public health priority, with the United States and Canada declaring a state of emergency due to rising death tolls from opioid abuse." Are you sure the US (i.e., the US federal government) declared the opioid crisis a state of emergency in 2016? There seem to have been some US states which did so on a state level, but as far as I know it has not yet been the case for the federal level (even though the Trump administration seems to consider it, see https://www.vox.com/policy-and-politics/2017/8/9/16118526/opioid-epidemic-national-emergency )

We have corrected this error in the Introduction (p. 4).

6. Page 2, line 4-6: "Reducing opioid prescribing among opioid-naïve patients at high-risk of developing subsequent addiction may reduce opioid use, and enable prioritization for alternative management strategies." As I understand your review, it's not just about identifying at-risk-individuals (to whom opioids should be prescribed only with extra caution) but also about prescriber- und system-level risk factors, which would not be addressed by reducing prescriptions to specific patients, but by system-level approaches. You might want to make this clearer here.

We have edited the Abstract (p. 2).

3. * Page 2, line 11-12: "We will also supplement our search with a scan of the gray literature to identify relevant ongoing studies." The main aim of searching grey literature is generally not only to identify ongoing studies (which you will also find in trial registries and conference abstracts), but to identify studies which have not been published in academic journals (even though they may already have been completed). Further down in the text you use the British English spelling (grey instead of gray) - you might want to stick to one of the two.

The suggested changes have been made (Abstract, p. 2).
7. Page 2, line 16: Why do you exclude patients receiving opioids for cancer pain? It makes sense to exclude palliative patients (a large portion of whom will be cancer patients), but why do you exclude cancer patients who are not on palliative care? Many of them may still have a considerable life span to live, and thus be at risk of suffering from opioid addiction after their cancer has been cured or contained. In case you stick to excluding cancer patients you should explain your rationale for doing so.

We agree with Reviewer #3 that cancer patients who survive treatment are at risk for addiction, if treated with prescribed opioids. However, in our clinical experience, the majority of severe cancer-related pain treated with opioids is caused by extensive tumour burden (e.g., resulting in nerve compression), or metastatic disease that is not curable, and generally not a prominent presentation of curable cancer. Also, it is rare for opioid-addicted cancer patients to turn to illicit substance misuse. We agree with the American Society of Clinical Oncology’s 2016 statement that cancer patients should be exempt from the US Federal government’s regulations restricting access to or limiting doses of prescription opioids to this special population, in order to ensure that cancer-related symptoms are adequately controlled.4 We have explained this rationale for this exclusion (Methods, p. 6)

8. Page 2, Line 19-20: "We will synthesize the effect sizes of individual risk factors derived from clinically homogenous studies with similar designs." I suppose that you will synthesize the results of all studies - you may synthesize those studies which are sufficiently homogenous with meta-analysis, and the remaining ones narratively (you might also choose to synthesize them graphically with harvest plots, which are a nice and innovative way to synthesize evidence from studies when meta-analysis is not feasible - see https://www.ncbi.nlm.nih.gov/pubmed/18298827 )

We have clarified in the Abstract (p. 2), and in our protocol (Methods, Data Synthesis, p. 12) that we will synthesize homogenous studies using random effects meta-analysis, and synthesize other data (insufficient for meta-analysis, or non-homogenous) qualitatively. We are intrigued by the idea of using Harvest plots, which we are inclined to use, if appropriate.

9. * Page 2/3, Line 21 ff: Here again you limit the discussion of the potential implications and uses of your review to patient-level risk factors, and the identification of at-risk-patients. You may want to broaden the scope to substance-, prescription-pattern-, prescriber- and system-level risk factors, and potential approaches to address these (such approaches would need, of course, to go beyond the identification of at-risk patients and the withholding of opioids from those).
We agree, and have edited the Abstract accordingly (p. 3)

10. Page 4, Line 4-5: "Unfortunately, the medical use of opioids can lead to addiction, dependence, or non-medical use. These are characterized by….". The sequence of these two sentences suggests that the characteristics listed in the second sentence apply both to addiction/dependence AND any form of non-medical use - which is, of course, not the case; the second sentence lists characteristics of addiction/dependence, but not necessarily of non-medical use in general. Please clarify.

We have corrected this (Introduction, p. 4).

11. * Page 4, line 8: "Addiction to opioids is associated with transition to injection drug use...". I suppose that what you want to say here is rather "Addiction to opioid analgetics / prescription opioids is associated with transition to the use of illegal opioid and non-opioid drugs, such as heroine"; Many (but not all) opioids are injection drugs, and vice versa, so the sentence as it stands is circular.

We have edited the manuscript (Introduction, p. 4).

12. * Page 4, line 8-11: "Addiction to opioids is associated with … mental health illness," Addiction to opioids is not only associated with mental illness, it is a mental illness; please consider rewording to "associated with mental co-morbidities" or "associated with further mental illnesses, such as depression etc."

We have edited the manuscript (Introduction, p. 4).

13. Page 4, line 11-13: While it is ok to focus the discussion on North America it might broaden the appeal and use of your review if you include a short paragraph on the international context, including the situation in Europe, among others.

Rising death rates from opioid use have been reported for the US and Canada, but to our knowledge not for European countries. Nonetheless, our review will aim to enrol studies internationally, and produce results that are generalizable to an international context. We have edited this sentence to broaden the focus of our review (Background, p. 4).
14. Page 4, line 17: "opioids continue to be the mainstay of treatment for acutely painful medical and surgical conditions." I suppose the word "acute" is used here in the sense of "very strong", and not as the opposite of "chronic"? Then you may want to write "very strong" (or something similar) instead of "acute", as the current wording might be misunderstood, in particular by non-native speakers.

The term acute refers to both very strong and non-chronic in this context. We believe the term is appropriate in this context, and have added examples to explain (p. 4). Our review is not about chronic serious pain, for which many more non-opioid alternatives exist, but about situations in which analgesia must be initiated in order for patients to be able to manage (e.g., dislocations, acute disc herniation).

15. Page 4, line 19-22: This discussion seems to focus on emergency settings, and on the treatment of acute (i.e. short-term) pain. Your review is, however, not limited to this, but also includes the long-term treatment of chronic pain, right? You might therefore want to broaden the discussion a bit here (e.g. by discussing alternative pain-relief strategies suitable for chronic pain, such as physiotherapy, psychotherapy, etc. - regional anaesthetic and ketamine will not be viable alternatives for most chronic pain patients). Moreover, the discussion is focused on patient-level risk factors - see my comment regarding this issue above.

Our focus is on non-chronic pain, and the initiation of opioids in patients presenting with sudden severe pain.

16. * Page 5, line 12-16: You may want to add prescription-pattern related risk factors to the list of risk factors you will look at - e.g. it might be that certain prescription patterns (relating to dosage, timing, dispensing mode, etc) are associated with a higher risk than others. Moreover, it might be helpful to provide the reader with examples for system-level risk factors.

We have made edits to this effect in the Methods section (Topic, p. 8).

17. Page 5, line 15-19: You may want to explain in greater detail how bullet point 1 (risk factors) and bullet point 2 (characteristics) differ, how you distinguish the two, and your rationale for doing so.

Risk factors will be reported using odds and risk ratios, and will indicate factors associated with the development of addiction. Characteristics of the clinical indication for, and of opioid
prescribers and prescriptions studied will describe the clinical contexts in which opioid prescribing occurred, and will allow readers to understand the results applicability to their context. Some identified characteristics may also be risk factors (e.g., type of medication prescribed). We have edited the first two bullets to clarify the rationale for both specific objectives (Objectives, p. 5/6).

18. Page 7, line 1-4: What is your rationale for defining opioid-naivety in the way you do it? Is there any established definition you could use as reference? The doses you define as threshold seem to be quite high for me, whereas the time span - one week - seems quite short, but I'm not an expert on this; if there is a good clinical, empirical or physiological justification for this definition this is fine, but you might want to mention this justification. Moreover, you may want to state that you exclude opioids not used for pain relief (in particular loperamid for diarrhea, and dihydrocodein for cough, both of which are used very widely in Europe, but are probably not relevant for your review).

The established thresholds were used as per the FDA’s definition of opioid tolerance. We have edited the manuscript to exclude opioids not used for pain relief, but have moved this section according to Reviewer 4’s suggestion (Methods, Sensitivity Analysis, p. 13).

19. Page 7, line 7-24: The different definitions and criteria of opioid addiction/dependence might be easier to follow if you present them as bullet-points, or in a table.

We have made reference to Appendix B where this information is listed in bullet point (Methods, p. 8).

20. * Page 8, line 3: "Included studies must report on at least one risk factor for opioid addiction, … ." How will you decide what counts as a risk factor? Anything described as such in the included studies? Or any factor described in the included studies as being associated with addiction/dependence? You may also spent some words on how you define the term "risk factor" (you list examples, but you do not provide a general definition), and whether you will try to distinguish risk factors for which there is evidence that they play a causal role in addiction, and risk factors for which it is more likely that they represent non-causal correlations only. (Distinguishing these two types of risk factors is, of course, crucial for designing appropriate prevention strategies).

We have defined risk factor (Methods, Topic, p. 8), and have added the concept of protective factors in the Objectives statement as we agree that both are important (p. 5).
21. * Page 8, line 7-9: "We will include observational and experimental studies, including randomized control trials and cross-sectional, prospective or retrospective cohort, or case-control studies." Will you include any kind of experimental studies, or only RCTs? In the latter case, what is your rationale for not including non-randomised intervention studies? There are non-randomised experimental study designs (mainly non-randomised controlled trials and interrupted-time series studies) which can provide better-quality evidence than purely observational studies, so excluding them while including observational studies doesn't seem to make sense, or is at least in need of a good justification. The Cochrane Effective Practice and Organization of Care (EPOC) Group provides some guidance on which non-randomised study designs may be included in systematic reviews (http://epoc.cochrane.org/resources/epoc-resources-review-authors) and you may also refer to Chapter 13 of the Cochrane Handbook for further guidance (http://handbook-5-1.cochrane.org/) - while your review is not a Cochrane review you may still find the information and guidance provided there helpful.

We will include all of the above-mentioned study designs, and have clarified this (Study Design, p. 9).

22. * Page 8, line 11-20: Most systematic review protocols I'm aware of include the full search strategy (at least for MEDLINE) - what is your rationale for including only a preliminary one? Developing the search strategy will in any case be the next step you need to take, so you might do it now and include it in the protocol (I'm not a search specialist, but other peer reviewers might be, so this might be a chance to get feedback on the exact search strategy, too).

We have included the final MEDLINE search (Appendix A, p. 21-23).

23. * Page 9, line 11-12: "We will search for studies citing all papers meeting our inclusion criteria using the Web of Science Core Collection and ScienceDirect (Elsevier)." Are you sure you mean ScienceDirect and not Scopus (also by Elsevier)? As far as I know ScienceDirect includes only journals published by Elsevier. In my experience Scopus is excellent for citing-studies searches, and has a good coverage. I haven't used the Web of Science Core Collection for citing-studies searches yet, but it might be sufficient to use one of the two databases (preferably the one with better coverage and functionality).

The University of British Columbia does not have a license for Scopus. Searching journal titles in Elsevier ScienceDirect will provide access to citing studies as does the Web of Science. Their
journal collections are different, so a journal article may be included in one but not the other. Searching both provides the best opportunity to find citing papers.

24. Page 9-10: You may want to organize the description of your searches in a more systematic, structured way, e.g. using the following sub-headings (currently these four different approaches are mixed up in your description of the search process, jumping forward and backward between them):

- Academic databases (MEDLINE, EMBASE, etc)
- Snowballing searches (i.e. citing- und cited-studies searches; both can be done through Scopus, and would replace the manual checking of reference lists of included studies)
- Ongoing studies (through trial registries and conference proceedings)
- Grey literature (through Google and the websites of medical associations, agencies and organizations)

We have presented our search in this manner (Methods, Information Sources, p. 9/10). As we are unable to use Scopus for cited and citing studies, we prefer to manually check reference lists of included studies to ensure we do not miss any papers.

25. Page 9: Will you also contact study authors (and possibly selected experts in the field) to identify further studies? This is a practice recommended by Cochrane, and may help to fill gaps left by the other search methods.

We will contact authors to identify further studies and have added this to the Methods section (Information Sources, p. 10).

26. Page 9: Will you de-duplicate the results of your search? You should, as it saves a lot of time, and you should describe how you will do it (in my experience, it can make sense to do multiple de-duplication rounds with different software applications, to ensure that as many duplicates as possible are removed; EndNote and Zotero are ok for deduplication, and RefWorks will probably also have such a functionality).

We have clarified that we will de-duplicate our searches (Data Management, p. 11).
27. Page 9: Which software will you use for title and abstract screening? I strongly recommend that you use specialized reference screening software for this purpose (doing it with a normal reference manager and MS Excel is burdensome and error-prone); in my experience, the best screening application is Rayyan, which is a free web application (https://rayyan.qcri.org/). Alternatives include Covidence (https://www.covidence.org/) and DistillerSR (https://www.evidencepartners.com/products/distillersr-systematic-review-software/), which can be used to streamline the whole systematic review production process; however, the last time I used them I found them less convenient for the title and abstract screening than Rayyan.

Thank you for pointing us to this software. We have started our work in Excel, and will continue with this program, as it will also allow us to record inclusion/exclusion criteria and establish kappa scores for between-rater agreement on inclusions and exclusions.

28. Page 9, line 9-10: "We will record the reason for exclusion for each record using Excel." Do you really want to do this? This is a lot of extra work, in particular if you have a lot of references to screen. I suggest that you document the reasons for exclusions only at the full-text screening stage, but not at the title/abstract screening stage.

We have clarified the documentation of exclusions for the full text phase. See edits to Methods (Data Management, p. 11).

29. Page 11, line 16 ff: Here you seem to equate risk of bias with methodological quality of a study, but the two are not the same (see Chapter 8 of the Cochrane Handbook for an explanation why the two are distinct: http://handbook-5-1.cochrane.org/). The assessment tool developed by Downs and Black is NOT a tool for risk of bias assessment, but one for the assessment of methodological quality (take for example the first item of the checklist, "Is the hypothesis/aim/objective of the study clearly described?" - a missing description of the hypothesis/aim/objective of a study does not necessarily affect its risk of bias). A tool which comes closer to the risk of bias assessment you have in mind might be the Quality appraisal checklist for quantitative studies reporting correlations and associations developed by NICE (https://www.nice.org.uk/process/pmg4/chapter/appendix-g-quality-appraisal-checklist-quantitative-studies-reporting-correlations-and), but there are certainly others which are suitable. Moreover, if you also include non-randomised intervention studies (which I recommend) you will need a tool suitable for those; you could used the EPOC-adapted Cochrane risk of bias tool (http://epoc.cochrane.org/resources/epoc-resources-review-authors), or the newly developed ROBINS-I tool (with which I have no experience so far - http://www.bmj.com/content/355/bmj.i4919)
Thank you for this suggestion. We proposed to use NICE tools for observational and intervention studies (Appendices D & E, p. 29-35).

30. * Page 13, line 1-6: Your dissemination plan is exemplary - the only thing you might want to add is a Review Advisory Group, i.e. a group of experts and practitioners in the field who can provide input at all stages of the review process, in particular at the beginning (refinement of the research questions etc.) and during dissemination.

We are fortunate to have clinicians in our study team who are acting in this capacity.

31. * Page 13, line 10-11: "We will synthesize all other data qualitatively." Please consider rewording to "synthesize narratively" - your main interest is in the effect size of various risk factors, so it is a quantitative review, even if you can't do a meta-analysis. For details on how to integrate qualitative evidence into a systematic review see Chapter 20 of the Cochrane Handbook (http://handbook-5-1.cochrane.org/). As mentioned above you may want to consider creating harvest plots in addition to the narrative synthesis (see https://www.ncbi.nlm.nih.gov/pubmed/18298827).

We have made the suggest change in wording (Data Synthesis, p. 13), and will look at using Harvest plots once we identify the types of data we will be synthesizing.

32. Page 13, line 10-11: You might add the following additional limitations: Limitation to publications in English, French and German; searches conducted in English only; inclusion of quantitative studies only; among others.

However, we have added these limitations (Limitations, p. 14).

33. * Page 13, line 14-15: "Potential impact: Up-to-date information on risk factors for opioid addiction among opioid-naïve patients who require opioids for pain control…". The review is not only relevant for patients who require opioids for pain control, but even more so for patients who may in practice receive opioids but for whom viable alternatives exist, right? So you may want to reword this sentence (e.g. by simply writing "patients receiving analgetics", or something similar).

We have made this change (Potential Impact, p. 15).

Page 13, line 17: "patients being newly prescribed opioids analgesics." See comment above.
We have edited this sentence (Potential Impact, p. 15).

Reviewer #4:

34. Please reference PRISMA guidelines under methods section and provide page numbers to the checklist in Appendix E.

We have referenced the PRISMA guidelines, and have added the page numbers to Appendix F (p. 36).

35. Please reference the POTS criteria

We adapted the Population, Intervention, Comparison and Outcome (PICO) framework for our systematic review, as we do not seek to synthesize information on the effectiveness of interventions. Instead, we propose to the following criteria: Population, Outcome, Topic, and Study selection (POTS), which are more relevant for studies reporting risk factors.

36. System-level risk factors are mentioned, however, it is unclear what these are even with the figure. Please clarify.

Please see our detailed response to comment 2, and edits to the manuscript to clarify this in the Methods (Topic, p. 8) to clarify.

37. Under the population heading there is information relating to sensitivity analysis and other statistical analysis. Please remove this and add to its own heading. This is not relevant to the inclusion criteria for the population.

We have created a separate heading for sensitivity analyses (Sensitivity Analysis, p. 13).

38. Why are RCTs included for a risk factor systematic review? What information will you be extracting from RCTs for risk?

We will include RCTs that examine opioid addiction as an outcome, and adjusted their results for prognostic covariates. Covariate adjustment is commonly done in RCTs to balance groups of patients for important prognostic covariates that could represent sources of bias. If positively or
negatively associated with the outcome, and their effect size is reported, RCTs could present data on risk factors of protective factors for opioid addition.

39. The data synthesis section requires more information. Will you be using odds ratios for the meta-analysis? What are the thresholds for heterogeneity?

Data on risk factors is most likely reported using odds ratios. We have added this to the protocol (Data Synthesis, p.12). Given the significant limitations, including lack of power, of statistical heterogeneity assessments, we will not use any numeric cut-offs, but instead will use our assessment of clinical heterogeneity to decide whether to pool studies or not.

40. What outcomes will be used for the summary of findings table?

Risk factors and protective factors will be reported using odds ratios as a measure of effect size.

41. What test will you be using for funnel plots?

We believe that funnel plots should primarily serve as visual aids for detecting bias, and that statistical tests should generally not be performed for funnel plot asymmetry. Given the unknown number of studies that will meet our inclusion criteria, and problems of statistical power and false positive results, we will use visual inspection of the plot to evaluate for asymmetry.

42. Search strategy line 3 why is there a time limit for these dates?

In MEDLINE the scope note for the MeSH term Analgesics, Opioid states that this term was previously indexed as Analgesics from 1966-1974. Consequently we have included analgesics for those years, as they are relevant to our search. If we did not include this term we would miss relevant results for those years.

References:


