Reviewer’s report

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

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Reviewer: Peter von Philipsborn

Reviewer's report:

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:

* 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 )

* 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- and 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.

* 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.

* 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.

* 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)

* 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).

* 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.

* 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.

* 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.

* 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.

* 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 anesthetic and ketamin 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.

* 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.

* 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.

* Page 7, line 1-4: What is your rationale for defining opioid-naivity 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).

* 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.

* 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).
* 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.

* 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).

* 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).

* 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):  
  o Academic databases (MEDLINE, EMBASE, etc)  
  o 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)  
  o Ongoing studies (through trial registries and conference proceedings)
Grey literature (through Google and the websites of medical associations, agencies and organizations)

* 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.

* 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).

* 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.

* 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.

* 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 use 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)

* 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.

* 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).

* 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.

* 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).

* Page 13, line 17: "patients being newly prescribed opioids analgesics." See comment above.

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