PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cannabinoids versus placebo or no intervention for pain. Protocol for a systematic review with meta-analysis and Trial Sequential Analysis
AUTHORS	Barakji, Jehad; Korang, Steven Kwasi; Feinberg, Joshua; Maagard, Mathias; Gluud, Christian; Mathiesen, Ole; Jakobsen, Janus

VERSION 1 – REVIEW

REVIEWER	Yury Khelemsky Icahn School of Medicine at Mount Sinai
REVIEW RETURNED	12-Jun-2019

GENERAL COMMENTS	P5 L 24 - change all non exhaustive lists (e.g. TEXT) to (i.e. TEXT, etc.) all instances of i.e. should be followed with etc. e.g should be used only when providing the ONLY specific example of a concept. Reformat tables - to better fit pages

REVIEWER	Kim Madden McMaster University, Canada
REVIEW RETURNED	21-Jun-2019

GENERAL COMMENTS	Thank you for the opportunity to review this protocol for a systematic review of cannabinoids for pain. This is an important emerging therapeutic area that is of great interest to many people, particularly given the "opioid epidemic" in North America and elsewhere. After reading this protocol manuscript, I have a few comments and questions for the authors. 1. The introduction contains a very thorough review of concepts relating to pain and the endocannabinoid system, but it does not really contain a rationale for why this review is needed. I think that an opening paragraph on the rationale for this review would help tell the story better. It seems to begin abruptly with a description of the many types of pain. 2. The section titled "Why it is important to do this review" doesn't make a strong case for why this review is required in addition to the ten previous reviews. Four reviews used a GRADE approach already, and most of the reviews seem like they are pretty good quality so what does this review add? If there are new RCTs that have come out since the previous reviews, then that would be a strong justification, but it is not clear that this is the case here. 3. The objective section should be more specific, using PICO format if possible. E.g. specify what is meant by "beneficial and harmful effects". Add secondary objectives as well.

	4. The section on comparison groups states that only placebo controlled trials and control groups of no intervention will be included. There are some trials of cannabinoids versus active comparators (NSAIDS, opioids etc.). Why are these not included? I think that comparisons to commonly used pain medications are the most useful comparisons. Additionally, comparisons to no intervention cannot be blinded and will be at high risk of bias. 5. Can you describe more in the section on patient engagement? What was the outcome of these consultations? Which outcomes were chosen by patient advocates? Did the investigators change any of their research plans based on patient input? 6. What is the rationale for having 4 primary outcomes? I would expect very few cannabis trials to report on mortality. Have the authors considered just having "pain" as the primary outcome and not specify VAS/NRS pain? There are a large number of cannabis trials that use other pain scales. The authors could use standard mean difference for all pain measures. The authors may also have a difficult time pooling harms results as they are currently defined because the harms reporting in cannabis trials is particularly poor. 7. The section on electronic searches needs more details, e.g. exact searches for at least one database. 8. The authors provide a good explanation of the minimally important difference for pain but not any other outcomes. 9. The authors state that they will conduct both random-effects and foxed-effects meta-analyses and select the most conservative result. This may result in type II errors. I recommend that the authors select random-effects or fixed-effects (using an appropriate clinical rationale) a priori and stick with that. 10. The authors selected 8 subgroup analyses to perform. This seems like a lot of subgroup analyses and it is likely that one or more of them will show a significant result by chance alone. I recommend that the authors go through the criteria for credible subgroup analyses and only select subgroups that will be highly credible (https://www.bmj.com/content/340/bmj.c117)

VERSION 1 – AUTHOR RESPONSE

Comments to reviewer: 1
COMMENT:Please state any competing interests or state ‘None declared’:none
RESPONS: competing interest is now stated as ’None declared’.

COMMENT: Reformat tables - to better fit pages
RESPONS: Beacuse of the width of the tabel it is very difficult to fit the tabel into regular pages in a Word-document however if one selects ”weblayout” in the bottom-bar of the Word document one is able to view the tabel in it’s full width.

Comments to reviewer: 2
COMMENT: The introduction contains a very thorough review of concepts relating to pain and the endocannabinoid system, but it does not really contain a rationale for why this review is needed. I think that an opening paragraph on the rationale for this review would help tell the story better. It seems to begin abruptly with a description of the many types of pain.
RESPONS: We have now shorten the introduction section significantly, and added an opening paragraph on the rationale of this review.

COMMENT: The section titled "Why it is important to do this review" doesn't make a strong case for why this review is required in addition to the ten previous reviews. Four reviews used a GRADE approach already, and most of the reviews seem like they are pretty good quality so what does this review add? If there are new RCTs that have come out since the previous reviews, then that would be a strong justification, but it is not clear that this is the case here.
RESPONS: We have sought to improve the rationale, and we now believe that it does state more clearly how this systematic review will advance the previous work.

COMMENT: The objective section should be more specific, using PICO format if possible. E.g. specify what is meant by "beneficial and harmful effects". Add secondary objectives as well.
RESPONS: The objective section has now been specified and a secondary objective is added.

COMMENT: Can you describe more in the section on patient engagement? What was the outcome of these consultations? Which outcomes were chosen by patient advocates? Did the investigators change any of their research plans based on patient input?
RESPONS: We have now described in more detail how the patient associations have been involved in our systematic review and what the outcome of involvement was.

COMMENT: The section on electronic searches needs more details, e.g. exact searches for at least one database.
RESPONS: We have now submitted the exact searches for all the mentioned databases in additional file 3.

COMMENT: The section on comparison groups states that only placebo controlled trials and control groups of no intervention will be included. There are some trials of cannabinoids versus active comparators (NSAIDS, opioids etc.). Why are these not included? I think that comparisons to commonly used pain medications are the most useful comparisons. Additionally, comparisons to no intervention cannot be blinded and will be at high risk of bias.
RESPONS: It is impossible to assess effect sizes (compared to no intervention/ placebo) when two active interventions are compared. It is, therefore, imperative as a first step to compare a given intervention with no intervention/ placebo. It is of course possible to blind participants if the control intervention is placebo/ active place. Cannabinoids versus active comparators is indeed highly relevant comparison and therefore we are planning to conduct another review concerning this issue in the future. This systematic review will hopefully enable us to identify the possible indications of cannabinoid medicine regarding pain based on its analgesic efficacy. Then we will explore the magnitude of this analgesic effect in comparison to other active comparators.

COMMENT: What is the rationale for having 4 primary outcomes? I would expect very few cannabis trials to report on mortality.
RESPONS: We have chosen these 4 primary outcomes because we believe these outcomes are the most patient important outcomes and assessing these outcomes cover a broad range of different aspects of the potential effects of cannabinoids. We aware of the possibility that only a few trials have reported on mortality however this is an outcome of utmost importance. In addition, a recently published systematic review showed an increased risk of acute coronary syndrome in participants that consume cannabis (Richards et al., 2019).
By including all-cause mortality in our systematic review, we might not have enough power to say anything however we might identify a pattern which will enable future trials to optimize their design.

COMMENT: The authors state that they will conduct both random-effects and fxed-effects meta-analyses and select the most conservative result. This may result in type II errors. I recommend that

the authors select random-effects or fixed-effects (using an appropriate clinical rationale) a priori and stick with that.
RESPONS:
”In a fixed-effect meta-analysis, the underlying assumption is that all of the included trials estimate the same intervention effect, i.e., differences in observed effects across trials are assumed to be caused by random error (‘play of chance’). In a random-effects meta-analysis, the underlying assumption is that the included trials do not estimate the same intervention effects – it is assumed that the estimates of individual trial intervention effects follow a normal or a log normal distribution. The most commonly used random-effects model is the DerSimonian and Laird model. However, the Hartung-Knapp-Sidik-Jonkman random-effects model assuming a t-distribution of log (RR) (for dichotomous outcomes) seems to be a more valid meta-analysis method. It is often likely that a given intervention will have different effects across the included trials depending on different forms of the interventions, different definitions of the outcomes, different types of included participants, etc. The random-effects model assumption will, therefore, often be more realistic than the fixed-effect model assumption. If there is absence of statistical heterogeneity (the between trial variance of the estimated intervention effects is close to zero), then the fixed-effect and the random-effects models will show identical results. If there is substantial statistical heterogeneity, the fixed-effect meta-analysis will, in some circumstances, show erroneous results because the between trial variance is not appropriately accounted for. In such a case, the random-effects meta-analysis result should be regarded as the main result. On the other hand, if one or two trials accounts for approximately 80% or more of the total weight in a fixed-effect meta-analysis, then the random-effects meta-analysis might show erroneous results because the larger trials with the greatest precision are inappropriately down-weighted. In such a case, the fixed-effect meta-analysis result should be regarded as the main result (Jakobsen et al., 2014)”.

In order to reduce the risk of type I errors, we will select the most conservative result as primary. Even if these two types of meta-analyses produce different results, it is highly likely that the two types of meta-analysis results still will be correlated which will limit the need for multiplicity adjustments (Jakobsen et al., 2014). Nevertheless, we will mention the increased risk of type I errors caused by the planned different analysis methods.

COMMENT: The authors selected 8 subgroup analyses to perform. This seems like a lot of subgroup analyses and it is likely that one or more of them will show a significant result by chance alone. I recommend that the authors go through the criteria for credible subgroup analyses and only select subgroups that will be highly credible (https://www.bmj.com/content/340/bmj.c117)
RESPONS: We are aware of the risk of statistical significance just by play of chance, and we will carefully discuss this increased risk of type I error. We have now deleted four out of the eight planned subgroup analyses.

We have also attached: Manuscript (revised), Manuscript with highlighted changes (revised).

We now hope that we have modified the manuscript to your satisfaction. If you continue to see issues we have overlooked, or we still need to engage, please let us know.

VERSION 2 – REVIEW

REVIEWER	Yury Khelemsky USA Icahn School of Medicine at Mount SInai
REVIEW RETURNED	21-Aug-2019

GENERAL COMMENTS	This is an important project, however simply publishing the methodology is premature. Once the review has been performed, it should be published along with the methods.

REVIEWER	Kim Madden McMaster University, Canada
REVIEW RETURNED	31-Jul-2019

GENERAL COMMENTS	Thank you, I believe the authors have addressed most of my comments. I have a few minor comments in sections that the authors added in this revision. 1. The last paragraph before the objectives states: "Compared to previous systematic reviews on cannabinoids, we want to assess the effects of all types of cannabinoid versus placebo or no intervention for all different forms of pain. This increases the power and precision over the overall analysis..." I don't agree that including various types of cannabis and indications will necessarily increase precision of the overall effect estimate. In fact, it might decrease precision by increasing clinical/methodological heterogeneity. I recommend rewording this slightly. 2. The authors state in their response document that "It is impossible to assess effect sizes (compared to no intervention/ placebo) when two active interventions are compared." They also noted that they would conduct another review comparing cannabis to active interventions. Did the authors consider conducting a network meta-analysis instead of conducting two separate reviews? 3. Nabiximols is misspelled "nabiximole" in the experimental intervention section.

VERSION 2 – AUTHOR RESPONSE

Comments to reviewer: 1
COMMENT: This is an important project, however simply publishing the methodology is premature. Once the review has been performed, it should be published along with the methods.

Our response: We strongly disagree. Predefining and publishing the methodology is essential and this in in accordance with the PRISMA/ SPIRIT/ CONSORT guidelines. In the systematic review we will refer to the published protocol and the methodology of the systematic review.

Comments to reviewer: 2
COMMENT: The last paragraph before the objectives states: "Compared to previous systematic reviews on cannabinoids, we want to assess the effects of all types of cannabinoid versus placebo or no intervention for all different forms of pain. This increases the power and precision over the overall analysis..." I don't agree that including various types of cannabis and indications will necessarily increase precision of the overall effect estimate. In fact, it might decrease precision by increasing clinical/methodological heterogeneity. I recommend rewording this slightly.

Our response: We completely agree with this statement and this sentence has now been reworded: “Depending on the data results provided by the included trials this could increase the power and precision of the overall analysis and make it possible to conduct subgroup analyses and sensitivity analyses that may identify pain areas where cannabinoid could be especially beneficial and cause the least harms”.

COMMENT: The authors state in their response document that "It is impossible to assess effect sizes (compared to no intervention/ placebo) when two active interventions are compared." They also noted that they would conduct another review comparing cannabis to active interventions. Did the authors consider conducting a network meta-analysis instead of conducting two separate reviews?
Our response: The network meta-analysis design is relatively new and many published network meta-analysis have several limitations (Faltinsen and colleagues, 2018).
1) The quality assessment of the included trials is more complicated in a network meta-analysis. If review authors simply assess overall quality of individual comparisons, different treatments are judged as equally biased, even though the opposite may be true (Puhan MA and colleagues, 2014)
2) In general, when combining indirect and direct evidence, the power and precision of treatment effect estimates may increase.
3) Sparse data and repeated significance testing may lead to random errors, which causes difficulties in interpreting the results of network meta-analysis. This is a general problem concerning frequent updates of reviews and meta-analyses, however, this problem is more pronounced in network meta-analyses.

We therefore believe our first step should be to assess the effects of cannabinoids versus placebo in a 'traditional' systematic review of randomised clinical trials. We will consider a network meta-analysis if our results of the systematic review indicate that cannabinoids are beneficial.

Furthermore, we have added the following subgroup-analysis:

- Trials at risk of vested interests compared to trial with no risk of vested interests

In order to explore the reason behind possible reporting/publication bias which could influence the certainty of evidence by GRADE assessment.

We have also attached: Manuscript (revised), Manuscript with highlighted changes (revised).

We now hope that we have modified the manuscript to your satisfaction. If you continue to see issues we have overlooked, or we still need to engage, please let us know.