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)	Canadian Clinical Practice Guidelines for the Use of Plant-Based Cannabis and Cannabinoid-Based Products in the Management of Chronic Non-Cancer Pain and Co-occurring Conditions: Protocol for a Systematic Literature Review
AUTHORS	Wright, Patrick; Walsh, Zach; Margolese, Shari; Sanchez, Tatiana; Arlt, Stephanie; Belle-Isle, Lynne; St.Pierre, Michelle; Bell, Alan; Daeninck, Paul; Gagnon, Marilou; Lacasse, Gary; MacCallum, Caroline; Mandarino, Enrico; Yale, Janet; O'Hara, James; Costiniuk, C

VERSION 1 - REVIEW

REVIEWER	Kevin F. Boehnke University of Michigan Medical School, United States
REVIEW RETURNED	12-Dec-2019

GENERAL COMMENTS	The authors present a protocol for a systematic review of using cannabis and plant-derived cannabinoids for managing chronic pain and co-occurring symptoms, with the goal of synthesizing evidence to help develop guidelines for proper use of plant-derived cannabinoids/cannabis in chronic pain management. The main problems I encountered in this manuscript were related to definitions. I believe I inferred correctly from the abstract and content, but more explicit definitions are required for this manuscript to be clear. 1) The authors say in the abstract that they are investigating cannabis and cannabinoid-based products. However, at the end of the introduction, they state that they are focusing on cannabis and cannabinoid-based products but not synthetic cannabinoids. As synthetic cannabinoids are indeed cannabinoid-based products, it would be clearer if the authors specifically said they would be examining plant-derived cannabinoid products in the abstract and throughout to ensure full clarity. For example, CBP could be defined from the get-go as “Cannabinoid based products derived from the cannabis plant”. 2) Will secondary outcomes be examined within standalone studies (e.g., effects of cannabinoids on anxiety), studies of cannabinoids being used to manage chronic pain (e.g., looking at anxiety as a secondary outcome in a pain clinical trial), or both? It’s not clear based on the text. The study criteria appears to clarify that it’s only

	within the context of chronic pain clinical trials, but it'd be useful to be crystal clear throughout. Some minor comments: Page 6-7: Descriptions of nabiximols and nabilone/dronabinol could be fleshed out to be more descriptive. E.g., "Extracts include nabiximols" could mention that this is a 1:1 THC:CBD sublingual spray. Page 7:" In contrast to the role of synthetic pharmaceutical-grade cannabinoids, a major knowledge gap relates to the use of cannabis and plant-derived cannabinoids in the management of chronic pain and co-occurring conditions". Nabiximols have been tested extensively (more frequently than synthetic cannabinoids), in chronic pain mostly of neuropathic origin. Page 7: "… which is compounded by the introduction of CBP into the panacea of therapeutic options". Do you mean pharmacopeia? Panacea implies a universal cure. Page 11, line 31: A couple typos: "cannabi*" and "endocannabi*" Page 11 line 43: Did the authors mean to say that Cannabis and cannabinoid research will be hand searched?

REVIEWER	Nicole Tang University of Warwick, UK
REVIEW RETURNED	22-Jan-2020

GENERAL COMMENTS	It is a well-developed protocol for a systematic review examining the use of cannabis and cannabinoid-based products in the management of chronic pain and co-occurring conditions. This is a timely topic and would be of interest to the readership of BMJ Open. An earlier version of the protocol has apparently been registered with PROSPERO (#135886), although I was unable to identify the protocol using the reference number provided or the title of the current paper. It would be helpful to have the long CRD reference number or title of the PROSPERO registration specified in the text for easy cross-referencing. It is unclear from the protocol submitted whether the review has started, is currently ongoing, or completed. Some of the suggestions below (especially those concerning the search strategies) may not apply if the review is at a post-literature search stage. 1. Title of the paper – it could benefit from greater specificity to accurately reflect the actual scope of the review. If I understand correctly, from p.8, the proposed review will examine plant-based cannabis and CBP products rather than synthetic, pharmaceutical grade cannabinoids. Similarly, from page 15 I understand that cancer-related pain is one of the exclusion criteria. If that's the case, it could be reflected in the title by using the term "chronic non-cancer pain" instead of just "chronic pain". 2. Background - The authors state that chronic pain often co-occurs with sleep disorders, anxiety, depression, post-traumatic stress disorder and substance use disorders etc. Please make sure references provided to support this statement cover all areas mentioned. 3. Background - clarification/elaboration/rephrasing is required for a few sentences: Page 6 - the sentence starting "In contrast, synthethic

	pharmaceutical-grade" is incomplete and disconnected from the next sentence. Page 7 - perhaps reword the phrase ""which is compounded by the introduction of CBP into the panacea of therapeutic options", which doesn't sound quite right to me. Page 7 - last paragraph - might it be possible to cite prevalence rates to support the first 2 sentences? Page 7 - "however it is not without risks…" It'd be helpful to outline the risks (or give examples). 4. Measures - Please clarify whether the primary and secondary outcome measures would be evaluated at multiple timepoints, and whether the measures will be treated as continuous or dichotomous variables. Are the sleep measures mentioned validated questionnaires? If so, please provide references. It'd also be important to specify which parameters of sleep as measured with EEG that the team will examine. 5. Search strategy - Please provide a justification for the selected timeframe (2001-2019). Why choose 2001 as the cut-off? 6. Search terms - They search terms cited are unlikely to pick up common chronic pain conditions such as arthritis, fibromyalgia, spinal cord injury, diabetic neuropathy etc. 7. Exclusion - Will studies be excluded based on research quality rating? 8. Data extraction and management - a bit more information about AE definition, management and record keeping procedure would be informative. 9. Page 16 - "Data will be extracted from reviews, including existing meta-analyses, using a standardized data extraction tool" - this practice appears to be inconsistent with what is specified in Table 1, in which it says "Studies that focus on cannabinoid mechanisms, commentary articles or clinical reviews will be excluded". 10. Will the team consider conducting an empirical meta-analysis? If so, what would be the criteria used to decide whether a meta-analysis would be performed? 11. Reference 33 appears erroneous. Please double check. 12. Conflicts of interest - Please provide more information on the nature of the businesses of the companies listed in this section (e.g., Canopy Growth Corporation, Tilray Inc.) so the reader is informed of any potential conflicts of interest.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Kevin F. Boehnke
Institution and Country: University of Michigan Medical School, United States
Please state any competing interests or state 'None declared': None

The authors present a protocol for a systematic review of using cannabis and plant-derived cannabinoids for managing chronic pain and co-occurring symptoms, with the goal of synthesizing evidence to help develop guidelines for proper use of plant-derived cannabinoids/cannabis in chronic pain management.

The main problems I encountered in this manuscript were related to definitions. I believe I inferred correctly from the abstract and content, but more explicit definitions are required for this manuscript to be clear.

1) The authors say in the abstract that they are investigating cannabis and cannabinoid-based products. However, at the end of the introduction, they state that they are focusing on cannabis and cannabinoid-based products but not synthetic cannabinoids. As synthetic cannabinoids are indeed cannabinoid-based products, it would be clearer if the authors specifically said they would be examining plant-derived cannabinoid products in the abstract and throughout to ensure full clarity. For example, CBP could be defined from the get-go as “Cannabinoid based products derived from the cannabis plant”.

Authors’ Response: We agree with the reviewer’s suggestion and now indicate that we are using the term CBP to refer to cannabinoid-based products derived from the cannabis plant. This is mentioned in the abstract, the introduction and is also specified at various points throughout the text.

2) Will secondary outcomes be examined within standalone studies (e.g., effects of cannabinoids on anxiety), studies of cannabinoids being used to manage chronic pain (e.g., looking at anxiety as a secondary outcome in a pain clinical trial), or both? It’s not clear based on the text. The study criteria appears to clarify that it’s only within the context of chronic pain clinical trials, but it’d be useful to be crystal clear throughout.

Authors’ Response: Yes, we plan to examine secondary outcomes within standalone studies as well as within studies of cannabinoids being used to manage chronic pain. We clarify this in the methods section and provide the specific examples provided by the reviewer to ensure this is clear to readers (top paragraph, p.17).

Some minor comments:
Page 6-7: Descriptions of nabiximols and nabilone/dronabinol could be fleshed out to be more descriptive. E.g., “Extracts include nabiximols” could mention that this is a 1:1 THC:CBD sublingual spray.

Authors’ Response: We now mention that an example of a nabiximol is Sativex, which is a 1:1 THC:CBD spray. We also mention that nabilone and dronabinol are synthetic products administered orally by capsule (top of p.7).

Page 7:” In contrast to the role of synthetic pharmaceutical-grade cannabinoids, a major knowledge gap relates to the use of cannabis and plant-derived cannabinoids in the management of chronic pain and co-occurring conditions”. Nabiximols have been tested extensively (more frequently than synthetic cannabinoids), in chronic pain mostly of neuropathic origin.

Authors’ Response: This last sentence has been changed to… “Extracts include nabiximols (Sativex®), a 1:1 tetrahydrocannabinol (THC):cannabidiol (CBD) sublingual spray. Synthethic pharmaceutical-grade cannabinoids include nabilone (Cesamet®) and dronabinol (Marinol®), synthetic products administered orally by capsule. A major knowledge gap relates to the use of

cannabis and plant-derived cannabinoids derived from the cannabis plant in the management of chronic pain and co-occurring conditions." (top of p.7).

Page 7: "… which is compounded by the introduction of CBP into the panacea of therapeutic options". Do you mean pharmacopeia? Panacea implies a universal cure.

Authors' Response: Yes, we have changed this word to "pharmacopeia."

Page 11, line 31: A couple typos: "cannabi*" and "endocannabi*"

Authors' Response: We verified with our librarian and this is the proper way to write the search terms.

Page 11 line 43: Did the authors mean to say that Cannabis and cannabinoid research will be hand searched?

Authors' Response: Yes, that is correct. We have corrected this error: "…this journal will be hand searched for studies that meet the inclusion criteria." (top of p.12).

Reviewer: 2
Reviewer Name: Nicole Tang
Institution and Country: University of Warwick, UK
Please state any competing interests or state 'None declared': None declared

It is a well-developed protocol for a systematic review examining the use of cannabis and cannabinoid-based products in the management of chronic pain and co-occurring conditions. This is a timely topic and would be of interest to the readership of BMJ Open. An earlier version of the protocol has apparently been registered with PROSPERS (#135886), although I was unable to identify the protocol using the reference number provided or the title of the current paper. It would be helpful to have the long CRD reference number or title of the PROSPERO registration specified in the text for easy cross-referencing.

Authors' Response: We have now included the PROSPERO registration number (after the abstract).

It is unclear from the protocol submitted whether the review has started, is currently ongoing, or completed. Some of the suggestions below (especially those concerning the search strategies) may not apply if the review is at a post-literature search stage.

Authors' Response: We clarify that the systematic review is ongoing. We have added to the end of the paper a section on "Study Status" which states "At the time of protocol publication, discussions within the evidence synthesis working group have resulted in the plan to summarize data from systematic reviews separately from the data from original research. This data will be presented to the guidelines writing committee, who will draft the guidelines." (p.21)

Title of the paper – it could benefit from greater specificity to accurately reflect the actual scope of the review. If I understand correctly, from p.8, the proposed review will examine plant-based cannabis and CBP products rather than synthetic, pharmaceutical grade cannabinoids. Similarly, from page 15 I understand that cancer-related pain is one of the exclusion criteria. If that's the case, it could be reflected in the title by using the term "chronic non-cancer pain" instead of just "chronic pain".

Authors' Response:

The title has been changed to “Canadian Clinical Practice Guidelines for the Use of Plant-Based Cannabis and Cannabinoid-Based Products in the Management of Chronic Non-Cancer Pain and Co-occurring Conditions:Protocol for a Systematic Literature Review”

2. Background - The authors state that chronic pain often co-occurs with sleep disorders, anxiety, depression, post-traumatic stress disorder and substance use disorders etc. Please make sure references provided to support this statement cover all areas mentioned.

Authors’ Response: We confirm that the references provided cover all areas mentioned in this statement.

3. Background - clarification/elaboration/rephrasing is required for a few sentences:
Page 6 - the sentence starting “In contrast, synthethic pharmaceutical-grade” is incomplete and disconnected from the next sentence.
“”
Authors’ Response: This has been corrected and now reads: “A major knowledge gap relates to the use of cannabis and plant-derived cannabinoids derived from the cannabis plant in the management of chronic pain and co-occurring conditions.” (top of p.7).

Page 7 - perhaps reword the phrase ”which is compounded by the introduction of CBP into the panacea of therapeutic options”, which doesn’t sound quite right to me.

Authors’ Response: We have changed the world “panacea” to “pharmacopoeia”

Page 7 - last paragraph - might it be possible to cite prevalence rates to support the first 2 sentences?

Authors’ Response:
This section now reads:
“The frequent co-occurrence of chronic pain and substance use disorders is often explained as patients’ self-medicating to manage living with chronic pain. Approximately 21-29% of individuals prescribed opioids for chronic pain misuse them, while 8-12% develop opioid use disorder.” CBP substitution for opioids is increasingly reported in the literature. The potential for CBP use as a drug-related harm reduction strategy is being recognized, however it is not without risks, as its use may be associated with an increased risk of relapse, for example.

Authors’ Response: We now provide examples of some potential risks, including risk of relapse when cannabis is used in the context of opioid dependence. We provide additional references:

Wasserman DA, Weinstein MG, Havassy BE, Hall SM. Factors associated with lapses to heroin use during methadone maintenance. Drug Alcohol Depend. 1998;52:183–92.

Balhara YP. Time to include buprenorphine-naloxone combination in the WHO Model List of Essential Medicines. J Opioid Manag. 2013;9:237.

4. Measures - Please clarify whether the primary and secondary outcome measures would be evaluated at multiple timepoints, and whether the measures will be treated as continuous or dichotomous variables. Are the sleep measures mentioned validated questionnaires? If so, please

provide references. It'd also be important to specify which parameters of sleep as measured with EEG that the team will examine.

Authors' Response: We will not know what the measures are until we perform the review. Therefore, we do not know which parameters of sleep on an EEG would be examined (for example). We would like to clarify that we are not performing a meta-analysis and will provide summaries of study findings and note the limitations, as opposed to finding a common metric.

5. Search strategy - Please provide a justification for the selected timeframe (2001-2019). Why choose 2001 as the cut-off?

Authors' Response: We now indicate, "Only studies published since 2001 will be included to focus the review on recent evidence. Since 2001 there have been technological advances and regulatory changes, such as the legalization of medicinal cannabis in Canada, that may have improved the quality of research."

6. Search terms - They search terms cited are unlikely to pick up common chronic pain conditions such as arthritis, fibromyalgia, spinal cord injury, diabetic neuropathy etc.

Authors' Response: As the systematic review has already started, we cannot modify our search strategy but we have listed this point as a potential limitation of the study: "Furthermore, our search terms may not enable us to pick up common chronic pain conditions such as arthritis, fibromyalgia, spinal cord injury, diabetic neuropathy."(p21)

7. Exclusion - Will studies be excluded based on research quality rating?

Authors' Response: Studies will only be excluded if they meet the exclusion criteria. We will not exclude studies based on poor research quality (top of p.13).

8. Data extraction and management - a bit more information about AE definition, management and record keeping procedure would be informative.

Authors' Response: We now indicate "Records of all searches will be kept on secure databases only accessible to the investigators. Records of all data extraction forms and consensus discussions will also be kept on the same databases." (page 17)
"We will also record adverse events as reported in individual studies, including the frequency and severity of cases when applicable. Adverse events will collectively be analyzed utilizing the World Health Organization (WHO) Toxicity grading scale for determining the safety of adverse events. (p.17)

9. Page 16 - "Data will be extracted from reviews, including existing meta-analyses, using a standardized data extraction tool" - this practice appears to be inconsistent with what is specified in Table 1, in which it says "Studies that focus on cannabinoid mechanisms, commentary articles or clinical reviews will be excluded".

Authors' Response: We clarify that reviews will be used to help us locate pertinent articles to examine individually, but we will not extract data specifically from the meta-analyses themselves. We clarify this in the table so it says "studies listed in meta-analyses" will be included.

10. Will the team consider conducting an empirical meta-analysis? If so, what would be the criteria used to decide whether a meta-analysis would be performed?

Authors' Response: No, we do not intend to conduct a meta-analysis. We now specify this at the top of p.18.

11. Reference 33 appears erroneous. Please double check.

Authors' Response: We confirm that this reference is incorrect and have removed it.

12. Conflicts of interest - Please provide more information on the nature of the businesses of the companies listed in this section (e.g., Canopy Growth Corporation, Tilray Inc.) so the reader is informed of any potential conflicts of interest.

Authors' Response: Additional information is now provided in this section. See revisions in track changes.

VERSION 2 - REVIEW

REVIEWER	Kevin F. Boehnke Anesthesiology Department, Chronic Pain and Fatigue Research Center, University of Michigan Medical School
REVIEW RETURNED	20-Mar-2020

GENERAL COMMENTS	Page 6: Cannabidiol is misspelled "cannabindiol" Page 7: Synthetic misspelled as "synthethic" Just to be clear, will nabiximols-based studies be included? On page 12, the authors write, "Based on the recommendations of the medical librarian, the terms "nabiximols" and "dronabinol" were included in the search strategy to ensure that we capture all relevant studies." This implies that nabiximols may not be included… Did the authors mean to say nabilone instead of nabiximols?

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Kevin F. Boehnke
Institution and Country: Anesthesiology Department, Chronic Pain and Fatigue Research Center, University of Michigan Medical School
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
Page 6: Cannabidiol is misspelled "cannabindiol"
Page 7: Synthetic misspelled as "synthethic"

Authors' response: These errors have been corrected.

Just to be clear, will nabiximols-based studies be included? On page 12, the authors write, "Based on the recommendations of the medical librarian, the terms "nabiximols" and "dronabinol" were included in the search strategy to ensure that we capture all relevant studies." This implies that nabiximols may not be included… Did the authors mean to say nabilone instead of nabiximols?

Authors' response: We already performed the search strategy as articulated. However, we have added the word "to screen" at the end of this sentence so that it is clear that we will be screening the retrieved studies to determine whether or not they meet the inclusion criteria. We also italicize the word "exclusively" to emphasize that studies focused only on synthetic cannabinoids, such as nabilone or dronabinol) will be excluded. We also added an additional sentence to ensure clarity, "As nabiximols contain plant derived cannabinoids, they will be included."

This section now reads:

Based on the recommendations of the medical librarian, the terms "nabiximols" and "dronabinol" were included in the search strategy to ensure that we capture all relevant studies to screen. However, studies focused exclusively on the efficacy of synthetic cannabinoids of pharmaceutical grade (such as nabilone or dronabinol) approved for human use will be excluded. As nabiximols contain plant derived cannabinoids, they will be included.