PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effects of medical and non-medical cannabis use in older adults: protocol for a scoping review
AUTHORS	Wolfe, Dianna; Corace, Kimberly; Rice, Danielle; Smith, Andra; Kanji, Salmaan; Conn, David; Willows, Melanie; Garber, Gary E; Puxty, John; Moghadam, Esther; Skidmore, Becky; Garritty, Chantelle; Thavorn, Kednapa; Moher, David; Hutton, Brian

VERSION 1 – REVIEW

REVIEWER	Kirsten Marchand The University of British Columbia (Vancouver) Canada
REVIEW RETURNED	11-Oct-2019

GENERAL COMMENTS	Manuscript number: bmjopen-2019-034301 Manuscript title: The effects of medical and non-medical cannabis use in older adults: protocol for a scoping review Thank you for the opportunity to review this well written scoping review protocol. There are a number of strengths to this protocol manuscript, including the importance of the research questions; the authors plan to consider both the 'beneficial' and 'harmful' effects; and the very detailed and sophisticated explanation of the planned methods. This will be a very informative protocol for future researchers considering the use of scoping reviews. I found few weaknesses or limitations as the protocol is currently written. As a reader without in-depth knowledge of this population or concept, I offer the following minor suggestions, listed by section, page and line numbers (derived from the compiled pdf). Abstract: Page 2 | The abstract in general is very clear, concise, and accurate with a excellent (and brief) framing of the problem. Page 2 Line 24 | The first research question clearly stems from the abstract's background, while the second question requires a bit more explanation. I presume these are factors or conditions that might help to interpret the harmful and beneficial effects of cannabis use in older adults. Perhaps this could be stated a bit more simply in the abstract, leaving the longer question for the end of the introduction? Introduction: In general, the introduction provides adequate framing and justification for the planned review.

	Page 5 Line 11-12 | "…given the ethics of conducting RCTs on illicit substances". This may be a difference in viewpoints, but the primary reason for not conducting RCTs is not necessarily the illicit nature of the substance, but that randomizing participants to a medication/drug for which there are known harms or limited knowledge about the harms is not ethical. There are a number of circumstances, even in Canada, in which RCTs have been conducted on illicit substances in spite of the illicit nature of the drug, but because it may bring benefits (diacetylmorphine, for example). Page 5 Line 22 | "…effects of aging process …in older adults …" This is the first time the authors refer to older adults in the main manuscript text. Please define here what age range this includes (i.e., > 50), and if available, provide a citation for this. I have not done work with this population and am unsure if there are universally understood classifications of 'younger', 'middle-aged' and 'older' adults. The next line suggests that some research is available on people 45 and older, is 45 years also a common cut-off? Page 7 Line 41 | "However, the literature related to this research is diverse and vast". I wonder if the authors could add here that this challenges or limits other systematic review methods, further justifying the appropriateness and need for the chosen scoping review methodology. Page 8 Line 9 | "What sources and types of evidence exist…" Please consider defining 'sources' and 'types'. Won't this be determined according to the eligibility criteria (i.e. systematic reviews, RCTs, NRS and observational studies)? Perhaps the authors are planning to examine the distribution of study types? Page 8 Line 19 | "Age: 50-64…" Earlier in the introduction, the authors referred to "45 and older". I suspect that in responding to my prior comment, the defining cut-offs will be more clear and congruent with the older adult age groupings as listed here. Methods and Analysis: Comments related to this section are quite minor, rather than substantial concerns about the proposed methodology. Page 10 Line 28 | "Current use will be variable…" Authors have very clearly defined their target population for this review. Could they briefly state here an example of why current use will be variable for readers who may be less familiar? For example, current use might be daily use, monthly use, etc. Page 10 Line 44 | "Comorbidities include cancer, chronic pain, …"

	Have the authors considered if they will include populations who are using other illicit substances (e.g., adults with opioid use disorder concurrently using cannabis). I see mention of other illicit substances in the concept and context, but not in the population and wonder how that will be handled. Page 13 Line 6 | "(based on our preliminary search)" Please guide the reader to the supplementary material and the preliminary search that was provided in Appendix 2. Page 13 Line 34 | "Preliminary basic searches …" For readers who might turn to this protocol for methodological notes, I wonder if it may be helpful to provide a brief statement about the anticipated timeline of this project? The size of the literature identified in the preliminary searches is quite large, and the screening and extraction plans appear quite detailed, given they might be revised during this iterative work. Patient and Public Involvement Page 22 Line 37 | Could the authors expand briefly on how input was initially sought and on what particular aspects of the design of the review did patients provide input upon? The Discussion section mentions a Peer Support Association that provided input on the questions and scope; was the same activity used to also collect patient input? Were these consultations mixed (i.e. members from the knowledge user groups and patient representatives)? Potential Limitations and Mitigation Strategies Page 23 Line 44 | Suggestion to add here that OSF will be used to record any changes made, increasing transparency related to the iterative nature of this work. Appendices Thank you for providing the appendices. These are very helpful for getting a sense of the data charting approach that will be taken given the vast information that is of interest. Page 34 Appendix 2 | I noted from here that the authors will also include qualitative methodologies (as part of the observational designs, I gather) and up to here, I was expecting their focus to be on quantitative designs. I wonder if that might be clarified earlier in the manuscript as that is useful information to consider when interpreting the scope of the planned work and data extraction procedures.

REVIEWER	Suzanne Nielsen Monash University, Australia I have no competing interests relating to this review. I have conducted unrelated research funded by Seqirus and Indivior in relation to opioid-related harm and treatment, and I have published a series of review relating to the therapeutic use of cannabinoids. Some of these reviews were funded by the Australian Government, and no industry funding was received in relation to this work.
REVIEW RETURNED	01-Dec-2019

GENERAL COMMENTS	Overall – the proposed review would address an important area – how effects of cannabinoids (positive and negative) may differ in older adults. I would welcome work that can synthesise evidence in this area and the rationale for such work is clear. Overall the protocol is clearly written. My main concern is that the proposed review is so broad – including all conditions, all products and medical and non-medical use – but that the methods as to how the authors will disaggregating each of these aspects could be described in more detail. For example, if I understand the proposed approach from the sample tables included there seems very different cannabis products grouped together (only two groupings are proposed, 'natural' and 'synthetic'), which might make it be hard to interpret the findings. More details on the planned methods may assist with this concern as perhaps the authors have already considered how they will address this but it was not clear to me reading the protocol. Specific queries: Queries relating to editors notes about review of study protocols – the requirement for dates to be in the manuscript is not addressed Query around conduct of a scoping review – in my understanding these are typically conducted to map what is known, and identify evidence gaps prior to there being sufficient data to conduct a systematic review. Given the large body of evidence in the area of cannabinoids (and a large number of high-quality systematic reviews being already published) I am curious about why the authors would not move to starting with a systematic review. The authors also state the scoping reviews do not require formal assessments of evidence quality. I believe as scoping review methodology has evolved, assessing the quality of the evidence has become more standard. A widely discussed limitation of much of the research around cannabinoids is the wide variation in the quality of the studies and the levels of evidence. Given this, it would seem appropriate that quality of evidence is considered. Item 12 on the PRISMA-SCR checklist refers to an appraisal of the sources of the evidence, I would have expected a stronger rationale for not doing an appraisal of the quality of the evidence on this topic. Age definition for the review – the abstract cites use of cannabinoids in those over 45 and 'older adults' , while the introduction refers to 'the proportion of middle-aged to older adults' and also 'those 45 years and older' and also refers colloquially to a 'baby boomer cohort', and also discusses 'older adults' experiencing some conditions with differing prevalence to 'younger adults' – overall I felt that a clear definition of what age group 'older adults' was referring to (i.e. a definition with a citation) is needed in the introduction. Including the evidence that supports a specific age cut-off and a scientific rationale for why the definition / age cut-off was clinically relevant to the use of cannabinoids would strengthen the proposed study. I would also suggest avoiding terms like 'baby boomer' that are not defined and that may not be understood in all languages. 50 years of age appears to be chosen to use in the review itself. A clear justification for this choice could be added. Minor point, but I would also suggest avoiding specific proprietary/brand names in the introduction (e.g. tetrabinex) where referring to a widely known ingredient (delta-9-THC) would be sufficient. Some statements in the introduction require a citation e.g. p6 generally older adults suffer from … and the prevalence of anxiety

	disorders is high' - perhaps also add detail as to the prevalence of anxiety is in older versus younger adults? The introduction refers to an unpublished paper (reference 24, which is noted to be under review and cannot be accessed) – if this reference must be included, can an accessible reference be given (e.g an available pre-review version that can be viewed online) rather than referencing unpublished work. A large list of sub-populations, concepts and contexts are listed on p8 – I was a bit unclear if the authors were proposing that they would conduct subgroup analysis for all of these groups or how these different characteristics (gender, race, frailty, consumption method etc) would be considered in the review. The information in bold italics on p10 seems to repeat the text above it – it wasn't clear why the information was repeated in bold italics where other key definitions were not similarly formatted. In general – there are a large number of broad outcomes for what is proposed to be disseminated in a single peer review publication. There have been numerous systematic reviews on many of the single aspects are proposed to be presented together in this one scoping review which made we wonder how a single evidence synthesis could meaningfully summarise the beneficial and harmful effects across all clinical conditions with all cannabinoid use, both therapeutic and recreational. I am wondered if what is proposed is feasible with this very broad focus, or if a series of more focused outputs would be better. On p13 the authors refer to working with an information specialist to develop a search strategy (i.e. this is described to happen in the future), however appendix 2 includes a search strategy – has the strategy been developed already or is this still to happen? I had expected that a published protocol for a review would publish the search strategy for transparency/reproducibility P15 – last para refers to 'both datasets' (the main dataset and the younger adult dataset) – i think this is the first time a younger adult dataset is mentioned – why are the authors using key words related to younger adults and adolescents in a review that focuses on older adults? Use of AI software (p18) – is this an established approach? Can a reference for where this approach has been has been previously been used/validated be supplied P21 – re appraisal of evidence – as noted above, evidence appraisal has become more common with scoping reviews – for such a controversial area of medicine / science I would recommend considering including an appraisal of the evidence P21 – 'outcome data will be presented with the cell colour indicating direction of effects' – will the effect size also be reported, as it is noted that often there are positive effects (e.g multiple systematic reviews identify that cannabinoids are effective for chronic pain, but the effects sizes usually very small (e.g. NNT of 22-24 - see Stockings et al and others) – making it important not just to identify if a positive or negative effect is detected, but if the size of that effect is clinically meaningful. Table 3 – I would suggest that more detail is needed to be extracted and presented on the cannabis product in these tables – there appear to be only two groupings 'natural' and 'synthetic' – does natural include extracts, including extracts that are CBD only – and would CBD only extracts be grouped with THC only extracts? These are very different products with different clinical and adverse effect profiles making it challenging if they are grouped together. Similarly, under 'synthetic' would this include everything from nabilone, dronabinol, and things like 'K2/spice'

	that are used recreationally/non-medically all together? Given these have very different harm profiles I wasn't sure how this would work. Would trying to condense such differing products into single categories result in an important loss of information that might make the results hard to interpret?

REVIEWER	Angela Haeny Yale School of Medicine
REVIEW RETURNED	10-Dec-2019

GENERAL COMMENTS	The objective of this study is to conduct a scoping review of the effects of cannabis use among older adults. The authors provide a strong rationale for the study and a thorough overview of the methodology to be used. The only minor suggestions I have is for the authors to reconsider the inclusion of grey literature (e.g., dissertations/theses) and consider including Google Scholar and CINAHL databases when conducting their literature search.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Thank you for the opportunity to review this well written scoping review protocol. There are a number of strengths to this protocol manuscript, including the importance of the research questions; the authors plan to consider both the 'beneficial' and 'harmful' effects; and the very detailed and sophisticated explanation of the planned methods. This will be a very informative protocol for future researchers considering the use of scoping reviews. I found few weaknesses or limitations as the protocol is currently written. As a reader without in-depth knowledge of this population or concept, I offer the following minor suggestions, listed by section, page and line numbers (derived from the compiled pdf).

Abstract:

Page 2 | The abstract in general is very clear, concise, and accurate with an excellent (and brief) framing of the problem.

- Response: We thank the reviewer for this thought.

Page 2 Line 24 | The first research question clearly stems from the abstract's background, while the second question requires a bit more explanation. I presume these are factors or conditions that might help to interpret the harmful and beneficial effects of cannabis use in older adults. Perhaps this could be stated a bit more simply in the abstract, leaving the longer question for the end of the introduction?

- Response: We have removed the detailed second question from the abstract and replaced it with a more general statement regarding subgroup data exploration that ties more naturally into the abstract for readers.

Introduction: In general, the introduction provides adequate framing and justification for the planned review.

- Response: We thank the reviewer for this thought.

Page 5 Line 11-12 | "…given the ethics of conducting RCTs on illicit substances".
This may be a difference in viewpoints, but the primary reason for not conducting RCTs is not necessarily the illicit nature of the substance, but that randomizing participants to a medication/drug for which there are known harms or limited knowledge about the harms is not ethical. There are a number of circumstances, even in Canada, in which RCTs have been conducted on illicit substances in spite of the illicit nature of the drug, but because it may bring benefits (diacetylmorphine, for example).

- Response: We agree that perceived harms of cannabis may have also limited rigorous testing and have added a phrase to include the reviewer's suggestion in the first paragraph of the introduction. We also feel that restricted access to cannabis (both pharmaceutical and recreational) may have reduced trialing of cannabis, prior to legalization.

Page 5 Line 22 | "…effects of aging process …in older adults …"
This is the first time the authors refer to older adults in the main manuscript text. Please define here what age range this includes (i.e., > 50), and if available, provide a citation for this. I have not done work with this population and am unsure if there are universally understood classifications of 'younger', 'middle-aged' and 'older' adults. The next line suggests that some research is available on people 45 and older, is 45 years also a common cut-off?

- Response: We share two thoughts in response to the reviewer's query here:
    - Some of our cited data within the submitted protocol is derived from Statistics Canada information, and 45+ years was sometimes the most relevant age group available in some of the work we have cited in terms of representing the elderly population; we do not believe this choice to be associated with a particular medical rationale, however it provides Canadian data of relevance for the planned research.
    - We define our criteria for 'older adults' in the methods, which we have chosen to be 50+ years of age. While an ideal selection for this population was to have been 65+ years based upon discussions with our knowledge users, they agreed that data for the current topic was likely often to be unavailable for this age group. They expressed interest to consider data from a slightly younger group of patients, chosen to be 50+ years based on discussions with them, to ensure more data could be collected. We have now described this consideration in the protocol's Discussion section in regard to challenges and mitigation strategies. Where data focused upon the age group of 65+ years is available, this will be noted in the review.

Page 7 Line 41 | "However, the literature related to this research is diverse and vast".
I wonder if the authors could add here that this challenges or limits other systematic review methods, further justifying the appropriateness and need for the chosen scoping review methodology.

- Response: We have added a comment regarding the reviewer's suggestion and have altered text within the paragraph to accommodate it. The related section now reads as follows: "*Cannabis research literature is diverse and vast, which challenges systematic review methods. A scoping review would collate and map the available research on cannabis effects in older adults, demonstrating what topic areas may have sufficient evidence for future systematic review. As well, collation and mapping of the research evidence is a first step for the purposes of informing care, developing policy, and directing future primary research efforts.*"

Page 8 Line 9 | "What sources and types of evidence exist…"
Please consider defining 'sources' and 'types'. Won't this be determined according to the eligibility criteria (i.e. systematic reviews, RCTs, NRS and observational studies)? Perhaps the authors are planning to examine the distribution of study types?

- Response: We thank the reviewer for this request. "Sources and types" has been removed from the review question in the Methods section to align it with the question presented in the abstract and our proposed methods.

Page 8 Line 19 | "Age: 50-64…"
Earlier in the introduction, the authors referred to "45 and older". I suspect that in responding to my prior comment, the defining cut-offs will be more clear and congruent with the older adult age groupings as listed here.

- Response: We have removed the sample age groups, as they were purely an example. We have replaced them with the comment "using older adult age groupings reported in the included literature."

Methods and Analysis: Comments related to this section are quite minor, rather than substantial concerns about the proposed methodology.

Page 10 Line 28 | "Current use will be variable…"
Authors have very clearly defined their target population for this review. Could they briefly state here an example of why current use will be variable for readers who may be less familiar? For example, current use might be daily use, monthly use, etc.

- Response: We have added in examples of "current use" definitions such that the sentence now reads as follows: "*The definition of "current use" will likely be variable across studies (e.g., daily,*

weekly, past-month, past-year)." We have added the word 'likely' to the sentence as while we expect this to be the case purely due to differences in authors' choices for study design and exposure assessment, at the protocol stage we cannot guarantee this is the case.

Page 10 Line 44 | "Comorbidities include cancer, chronic pain, …"
Have the authors considered if they will include populations who are using other illicit substances (e.g., adults with opioid use disorder concurrently using cannabis). I see mention of other illicit substances in the concept and context, but not in the population and wonder how that will be handled.

- Response: Use of other substances (e.g., tobacco, alcohol, illicit drugs) is not part of our eligibility criteria (i.e., data from patients associated with use of other substances will be allowed in the review). We clarified this in the initial description of "Participants."

Page 13 Line 6 | "(based on our preliminary search)"
Please guide the reader to the supplementary material and the preliminary search that was provided in Appendix 2.

- Response: We have added in "see Appendix 2" in this section now to make this more clear for readers.

Page 13 Line 34 | "Preliminary basic searches …"
For readers who might turn to this protocol for methodological notes, I wonder if it may be helpful to provide a brief statement about the anticipated timeline of this project? The size of the literature identified in the preliminary searches is quite large, and the screening and extraction plans appear quite detailed, given they might be revised during this iterative work.

- Response: We have added in a clarification of the timeline for completion in brackets in this section, which reads as follows: "*We will work closely with an experienced information specialist to iteratively develop a search strategy that will balance the need for inclusivity with the need to yield a citation volume that will be manageable with current reference management software, within the budgetary and time constraints of the review (estimated timeline: one year for completion).*"

Patient and Public Involvement
Page 22 Line 37 | Could the authors expand briefly on how input was initially sought and on what particular aspects of the design of the review did patients provide input upon? The Discussion section mentions a Peer Support Association that provided input on the questions and scope; was the same activity used to also collect patient input? Were these consultations mixed (i.e. members from the knowledge user groups and patient representatives)?

- Response: We're happy to clarify this for the reviewer. For this project, Gordon Garner is an individual with lived experience in substance addiction who is the Executive Director of the Community Addictions Peer Support Association in Ottawa, Canada. Investigators from the research team work met regularly with him on research initiatives and discussed this work with him to seek input during the planning stages. Additional input from other individuals with lived experience was not sought during this component of the design phase. Input from other key stakeholders representing ongoing initiatives related to addiction and seniors' health included the Canadian Society of Addiction Medicine, the Canadian Coalition for Seniors' Mental Health, the National Initiative for the Care for the Elderly, the Seniors Health Knowledge Network, Public Health Ontario and Ottawa Public Health. We have adjusted the text in this section to read as follows: "*In planning this research, input was sought from multiple patient organizations during the preparation phase regarding elements of its design to ensure its findings would be of relevance to multiple groups including those with lived experience as well as stakeholders actively engaged in initiatives related to seniors' health.*"

Potential Limitations and Mitigation Strategies
Page 23 Line 44 | Suggestion to add here that OSF will be used to record any changes made, increasing transparency related to the iterative nature of this work.

- Response: Thanks for the suggestion. We have added a line regarding this adjustment.

Appendices
Thank you for providing the appendices. These are very helpful for getting a sense of the data charting approach that will be taken given the vast information that is of interest.

- Response: We thank the reviewer for the comment.

Page 34 Appendix 2 | I noted from here that the authors will also include qualitative methodologies (as part of the observational designs, I gather) and up to here, I was expecting their focus to be on quantitative designs. I wonder if that might be clarified earlier in the manuscript as that is useful information to consider when interpreting the scope of the planned work and data extraction procedures.

- Response: We appreciate this request from the reviewer. Qualitative designs are indeed excluded from the review. However, we retained certain terms as part of the grander search in order to also screen for some qualitative information that will be relevant for a separate research project.

Reviewer: 2

Overall – the proposed review would address an important area – how effects of cannabinoids (positive and negative) may differ in older adults. I would welcome work that can synthesise evidence in this area and the rationale for such work is clear. Overall the protocol is clearly written. My main concern is that the proposed review is so broad – including all conditions, all products and medical and non-medical use – but that the methods as to how the authors will disaggregating each of these aspects could be described in more detail. For example, if I understand the proposed approach from the sample tables included there seems very different cannabis products grouped together (only two groupings are proposed, 'natural' and 'synthetic'), which might make it be hard to interpret the findings. More details on the planned methods may assist with this concern as perhaps the authors have already considered how they will address this, but it was not clear to me reading the protocol.

- Response: We appreciate the reviewer's perspectives on the importance of this work. The reviewer is correct in commenting on the broad nature of this review, however we emphasize that this is the rationalization for the performance of a scoping review rather than a systematic review. Scoping reviews are a much less deep dive into the details of the evidence, allowing for the structured identification of areas where full systematic reviews could later be performed (i.e. finding areas with available evidence) and areas where primary research must be prioritized; we have now completed much of the data collection for this review, and we can comment clearly that the prioritization piece will be important messaging in the final review. The reviewer is also correct that the sample tables were broad and did not differentitate cannabinoids; another core feature of scoping reviews is their flexibility in establishing best ways to present evidence, and we can also clarify that the final review will be more in-depth distinguishing between cannabinoids based on input from our experts. The approach will be taken to best identify strengths and gaps of the available research.

Specific queries:

Queries relating to editors notes' about review of study protocols – the requirement for dates to be in the manuscript is not addressed.

- Response: we thank the reviewer for this request. At the time of the study start, a formal cut-off date had not been selected. Based on volume, we subsequently established that data from 2000 onward was a reliable cut-off which was also agreed upon as providing strong coverage of anticipated data from our clinical team members. We will rationalize this date and also include the date of the search being run in the completed review to ensure all information is available for readers.

Query around conduct of a scoping review – in my understanding these are typically conducted to map what is known, and identify evidence gaps prior to there being sufficient data to conduct a systematic review. Given the large body of evidence in the area of cannabinoids (and a large number of high-quality systematic reviews being already published), I am curious about why the authors would not move to starting with a systematic review.

- Response: We appreciate the reviewer's inquiry. The amount of evidence available regarding the effects of cannabis/cannabinoids in older adults is in fact not at all well known, as experts on our team have previously noted elderly individuals have often been excluded from past studies or their degree of representation in studies unclear/not reported. A scoping review was thus necessary to understand the extent of evidence available for the elderly in the medical and non-medical settings to establish what reviews may be feasible, and more importantly to identify current gaps for which our knowledge user partners may wish to soon consider offering funding opportunities for primary research. Thus, the scoping review approach was considered to be helpful; we have now clarified this in the protocol in the Discussion section as well by adding the following sentence: "*Based upon discussion amongst research team members, a scoping review approach (as opposed to a systematic review) was unanimously considered most*

appropriate based upon the current uncertainty regarding the availability and nature of evidence of cannabis use specific to the population of older adults."

The authors also state the scoping reviews do not require formal assessments of evidence quality. I believe as scoping review methodology has evolved, assessing the quality of the evidence has become more standard. A widely discussed limitation of much of the research around cannabinoids is the wide variation in the quality of the studies and the levels of evidence. Given this, it would seem appropriate that quality of evidence is considered. Item 12 on the PRISMA-SCR checklist refers to an appraisal of the sources of the evidence, I would have expected a stronger rationale for not doing an appraisal of the quality of the evidence on this topic.

- We appreciate the reviewer's perspective, and agree there is some evolution toward quality appraisal in scoping reviews, however this remains uncommon practice at this time; our approach includes quality appraisal of all systematic reviews using the AMSTAR-2 tool, while not including them for primary studies for reasons of budget and timeliness (and given this has not yet become fully engrained in these reviews). We note this plan under the protocol methods heading "*Critical appraisal of included evidence sources.*" In the Canadian context (we are uncertain if relevant in other countries as well), scoping reviews funded by health research organizations commonly have a lower maximum available amount compared to systematic reviews, and this represents an additional rationale as to why quality assessment of all studies is not always possible.

Age definition for the review – the abstract cites use of cannabinoids in those over 45 and 'older adults' , while the introduction refers to 'the proportion of middle-aged to older adults' and also 'those 45 years and older' and also refers colloquially to a 'baby boomer cohort', and also discusses 'older adults' experiencing some conditions with differing prevalence to 'younger adults' – overall I felt that a clear definition of what age group 'older adults' was referring to (i.e. a definition with a citation) is needed in the introduction. Including the evidence that supports a specific age cut-off and a scientific rationale for why the definition / age cut-off was clinically relevant to the use of cannabinoids would strengthen the proposed study. I would also suggest avoiding terms like 'baby boomer' that are not defined and that may not be understood in all languages. 50 years of age appears to be chosen to use in the review itself. A clear justification for this choice could be added.

- Response: We appreciate the reviewer's request for clarity here. Several steps have been taken:
    - The premise of older adults experiencing some conditions with different prevalence than younger adults relates to conditions such as reduced executive function, reduced attention/cognition and reduced memory, which are associated with reduced function and can be influenced by factors such as cannabis consumption. Changes in brain structure that occur with increasing age, such as alterations in grey and white matter and the potential for neurotransmitter that impact these structural changes to be impacted by substance use also add additional rationale for the specific interest in older adults. For these reasons, the older population is of interest to many stakeholders, including our knowledge users for this research. Relevant citations include:
        - Flint, A, Merali, Z & Vaccarino, F. Substance use in Canada: improving quality of life: substance use and aging. (Canadian Centre on Substance Use and Addiction., 2018).
        - Kelleher, L. M., Stough, C., Sergejew, A. A. & Rolfe, T. The effects of cannabis on information processing speed. Addict Behav 29, 1213–1219 (2004).
        - Ranganathan, M. & D'Souza, D. C. The acute effects of cannabinoids on memory in humans: a review. Psychopharmacology (Berl.) 188, 425–444 (2006).
    - As clarified in a response to Reviewer 1 above, our collaborating knowledge users were most interested in data regarding individuals aged 65+ years, but they agreed with the research team that data focused only to this group may not be commonly available. Out of concerns data for this group alone may be sparse and to allow for broader inclusiveness as to individuals approaching increased age, the cutpoint of 50+ years was felt by the team to offer a more conservative approach to the literature to be reviewed. Given this rationale, we have not added a specific citation to the protocol identifying why the age of 50+ years is pivotal. We now mention the rationale for this choice of 50+ years in the discussion section within the section discussing potential challenges and mitigation strategies: "*Regarding the minimum age criteria to be used*

for this review (50+ years), this value was selected by the research team following discussions wherein there was a consensus anticipation that there may exist limited data in adults aged 65+ years. A reduction in the minimum age criteria was considered to allow for a conservative approach to include more data related to the group of older adults." Where data focused upon the age group of 65+ years is available, this will be noted in the review.
    - We have removed language such as 'baby boomers' as suggested.

Minor point, but I would also suggest avoiding specific proprietary/brand names in the introduction (e.g. tetrabinex) where referring to a widely known ingredient (delta-9-THC) would be sufficient.

- Response: we have now adjusted the manuscript to avoid brand names as suggested.

Some statements in the introduction require a citation e.g. p6 generally older adults suffer from … and the prevalence of anxiety disorders is high' - perhaps also add detail as to the prevalence of anxiety in older versus younger adults?

- Response: we appreciate the reviewer's request for information here. We have added two references as suggested for this information in the background section of the protocol:
    - Lyness JM, Caine ED, King DA, Cox C, Yoediono Z. Psychiatric disorders in older primary care patients. J Gen Intern Med 1999;14:249–54. https://doi.org/10.1046/j.1525-1497.1999.00326.x.
    - Ward BW, Schiller JS. Prevalence of Multiple Chronic Conditions Among US Adults: Estimates From the National Health Interview Survey, 2010. Prev Chronic Dis 2013;10:120203. https://doi.org/10.5888/pcd10.120203.

The introduction refers to an unpublished paper (reference 24, which is noted to be under review and cannot be accessed) – if this reference must be included, can an accessible reference be given (e.g an available pre-review version that can be viewed online) rather than referencing unpublished work.

- Response: we're happy to report that the manuscript in question is one which we have now formally published since submission of this protocol; the full citation is now provided for the publication in Systematic Reviews (a BMC Journal).

A large list of sub-populations, concepts and contexts are listed on p8 – I was a bit unclear if the authors were proposing that they would conduct subgroup analysis for all of these groups or how these different characteristics (gender, race, frailty, consumption method etc) would be considered in the review.

- Response: we have adjusted the text to provide more clarity on this point; our intent was to 'map' the availability of information/outcome data related to these different subgroups and characteristics. This is valuable information with regard to the performance of future systematic reviews in terms of feasibility, and also can be valuable in guiding future funding opportunities for primary research for our knowledge users (i.e., emphasizing to researchers this data is needed).

The information in bold italics on p10 seems to repeat the text above it – it wasn't clear why the information was repeated in bold italics where other key definitions were not similarly formatted.

- Response: We appreciate the reviewer's request for clarity. We felt that, for clarity, the section regarding population was well served with a summative statement regarding how the population was to be defined for this review. The italicized font has been included to draw clear attention to this summary material.

In general – there are a large number of broad outcomes for what is proposed to be disseminated in a single peer review publication. There have been numerous systematic reviews on many of the single aspects are proposed to be presented together in this one scoping review which made we wonder how a single evidence synthesis could meaningfully summarise the beneficial and harmful effects across all clinical conditions with all cannabinoid use, both therapeutic and recreational. I wondered if what is proposed is feasible with this very broad focus, or if a series of more focused outputs would be better.

- Response: We thank the reviewer for requesting clarity here. We will reiterate two important points here that are relevant to keep in mind with regard to the planned work: (1) our approach for this work is a scoping review rather than a systematic review, and a key difference is in the approach to synthesis which involves a greater amount of mapping and summarizing directions in findings as opposed to performing and presenting formal meta-analyses and/or detailed narrative summaries of study findings; (2) while many of the outcomes of interest have been looked at in other reviews, few to none have been conducted with a focus on elderly patients,

where we received universal input from knowledge users and clinicians during the design phase that this data has been rarely and poorly looked at. As we have now completed data collection for the review and are presently synthesizing the evidence, we can comment that this intuition was correct, and we can confirm that presenting all of the evidence in a well-structured review article will be feasible. We will have data from a total from 95 articles, however the amount of information that can be pulled with regard to the elderly population in several of these articles is quite limited.

On p13 the authors refer to working with an information specialist to develop a search strategy (i.e. this is described to happen in the future), however appendix 2 includes a search strategy – has the strategy been developed already or is this still to happen? I had expected that a published protocol for a review would publish the search strategy for transparency/reproducibility

- Response: the included search strategy was already developed with the information specialist; we have adjusted the tense of this information such that this is more clear.

P15 – last para refers to 'both datasets' (the main dataset and the younger adult dataset) – i think this is the first time a younger adult dataset is mentioned – why are the authors using key words related to younger adults and adolescents in a review that focuses on older adults?

- Response: We're happy to clarify this for the Reviewer. To gain efficiencies in title/abstract screening, a structured approach was planned. After the literature search is completed and its citations retrieved by the information specialist, we will divide this full set into those that were more and less likely to pertain to older adults by categorizing citations by whether or not they mentioned terms such as adolescents and young adults. While all citations will be screened using the same methods, this allowed us to screen those anticipated to be less probable of being included after those anticipated to be more probable of being included. This was done to gain efficiencies in screening and data collection (i.e. to gather data to allow synthesis to begin earlier).

Use of AI software (p18) – is this an established approach? Can a reference for where this approach has been has been previously been used/validated be supplied?

- Response: We're happy to comment on this detail for the Reviewer. Much research on the use of AI for screening in systematic reviews has been published in the past few years in both journals related to knowledge synthesis as well as computer science. The knowledge synthesis community as a whole has not yet agreed upon a standard approach. Our approach in this case was designed to be conservative while still offering certain efficiencies given our large volume of citations; in no case will the AI make final decisions as to the inclusion or exclusion of a study for the review, however it operates in essence like a second screener in cases where a citation is judged to be either of very high probability to be relevant or of very low probability; all other citations are screened using a typical approach. For context, we feel it is worth noting that the use of AI methods for screening is currently expanding in the realm of systematic reviews, in particular in cases of reviews with large citation counts and the needs of knowledge users to have evidence for rapid decision-making needs. We now make a short mention of this fact in the discussion section (specifically the section on challenges and mitigation strategies) as follows, including citations: "*The use of AI for screening in systematic reviews has become of considerable interest in recent years [42,43], particularly in the presence of large citation volumes [44], and we will employ a conservative approach wherein this tool will not be responsible for any final decisions as to the inclusion status of a study.*"

P21 – re appraisal of evidence – as noted above, evidence appraisal has become more common with scoping reviews – for such a controversial area of medicine / science I would recommend considering including an appraisal of the evidence.

- Response: we appreciate the reviewer's suggestion. As mentioned above, we have included appraisal of systematic reviews with AMSTAR-2 in our work, while primary studies were not appraised for reasons of budget and timeliness. In large scoping reviews, evidence appraisal is not yet a very established component in practice and both budget and timelines can be rate limiting factors for researchers and funders.

P21 – 'outcome data will be presented with the cell colour indicating direction of effects' – will the effect size also be reported, as it is noted that often there are positive effects (e.g multiple systematic reviews identify that cannabinoids are effective for chronic pain, but the effects sizes usually very small (e.g.

NNT of 22-24 - see Stockings et al and others) – making it important not just to identify if a positive or negative effect is detected, but if the size of that effect is clinically meaningful.

- Response: We appreciate the request for information. The final review will be focused at this stage upon mapping the availability of treatment effects for different outcomes as well as their directions, but not their corresponding magnitudes. This is a common mapping element for outcomes in large scoping reviews, and it will allow us to further focus next steps of this research in collaboration with our knowledge users wherein they will help to select the areas for which further focus (and details to be addressed in full systematic reviews or new primary research) will be undertaken in subsequent research. If time and funds remain at the conclusion of the review, incorporation of effect sizes will be a primary focus for the research team.

Table 3 – I would suggest that more detail is needed to be extracted and presented on the cannabis product in these tables – there appear to be only two groupings 'natural' and 'synthetic' – does natural include extracts, including extracts that are CBD only – and would CBD only extracts be grouped with THC only extracts? These are very different products with different clinical and adverse effect profiles making it challenging if they are grouped together. Similarly, under 'synthetic' would this include everything from nabilone, dronabinol, and things like 'K2/spice' that are used recreationally/non-medically all together? Given these have very different harm profiles I wasn't sure how this would work. Would trying to condense such differing products into single categories result in an important loss of information that might make the results hard to interpret?

- Response: We're happy to address this query. We do intend to provide additional detail regarding specific cannabis products in the final review (e.g. with regard to specific synthetics and use for different reasons), and this will be driven by the availability/distribution of data (a plan given the flexibility afforded by the scoping review approach). This will allow for consideration of higher grouped information as well as more detailed information, as well as products with and without much evidence available in the literature. This will be of interest to our knowledge users and other researchers more broadly.

Reviewer: 3

The objective of this study is to conduct a scoping review of the effects of cannabis use among older adults. The authors provide a strong rationale for the study and a thorough overview of the methodology to be used. The only minor suggestions I have is for the authors to reconsider the inclusion of grey literature (e.g., dissertations/theses) and consider including Google Scholar and CINAHL databases when conducting their literature search.

- Response: We appreciate the reviewer's response. With regard to grey literature, at this time we have omitted this from our plan due mainly to the limitations of available funding as well as timeliness for our knowledge users (our search identified >30,000 citations); our intent is to re-visit remaining funds and time once we complete synthesis of the data from peer reviewed sources, and grey literature searching of targeted websites will be added as a post-hoc protocol inclusion if sufficient resources remain. With regard to considering Google Scholar and CINAHL as data sources, Google Scholar is a source of grey literature that we would cover if this aspect of searching (as noted earlier) is feasible based on remaining budget and time; regarding CINAHL, our information specialist felt strongly this data source would add little value and more noise to the search results given the databases already covered, and we trusted this perspective given her many years of experience developing searches for knowledge syntheses.

VERSION 2 – REVIEW

REVIEWER	Kirsten Marchand The University of British Columbia, Canada
REVIEW RETURNED	22-Jan-2020

GENERAL COMMENTS	Thank you for the opportunity to review this revised manuscript. The authors have thoughtfully addressed my comments and questions. I have no further queries.

REVIEWER	Suzanne Nielsen Monash University, Australia

	None relating to the topic of the review. Previous research funding from Indivior and Sequris and honoraria to present training on opioid dependence received by institution from Indivior.
REVIEW RETURNED	14-Jan-2020

GENERAL COMMENTS	Thank you for the thoughtful responses to the reviewers, the authors have clearly explained rationale for the approach and I have no further comments or queries relating to the protocol. I look forward to reading the review when it is available.