Author’s response to reviews

Title: Effectiveness of stop smoking interventions among adults: protocol for an overview of systematic reviews and an updated systematic review

Authors:

Mona Hersi (mhersi@ohri.ca)
Gregory Traversy (gregory.traversy@canada.ca)
Brett Thombs (brett.thombs@mcgill.ca)
Andrew Beck (abeck@ohri.ca)
Becky Skidmore (bskidmore@rogers.com)
Stéphane Groulx (stephane.groulx.agence16@ssss.gouv.qc.ca)
Eddy Lang (Eddy.Lang@albertahealthservices.ca)
Donna Reynolds (donna.reynolds@utoronto.ca)
Brenda Wilson (bwilson@mun.ca)
Steven Bernstein (steven.bernstein@yale.edu)
Peter Selby (peter.selby@camh.ca)
Stephanie Johnson-Obaseki (sjohnsonobaseki@gmail.com)
Douglas Manuel (dmanuel@ohri.ca)
Smita Pakhale (spakhale@toh.ca)
Justin Presseau (jpresseau@ohri.ca)
Susan Courage (susan.courage@canada.ca)
Brian Hutton (bhutton@ohri.ca)
Beverley Shea (bshea@ohri.ca)
Vivian Welch (vwelch@campbellcollaboration.org)
Matt Morrow (matt.jw.morrow@gmail.com)
Author’s response to reviews:

Handling editor

Hersi et al. have proposed an overview of review of the effectiveness of stop smoking interventions among adults and an update of a systematic review on electronic cigarettes. The methodology is well documented and shows the difficulty in following one set of a priori set of rules when undertaking overviews. Having said that, the reviewers have done a good job in documenting their intended methods with references to support their suggested steps.

Abstract: Line 66, you describe the review that will be updated in the second stage as the "most recent, comprehensive and high quality systematic review". The most recent review might not be the most comprehensive or the most high quality. So, what the priority: most recent, most comprehensive or most high quality? Does one trump the others, etc. You explained this in the methods but can you elaborate a bit more in the abstract.

Response: In respect of journal word count limits, we will be unable to add this detail to the abstract. However, as the information presented as-is may cause confusion for readers, and to reduce word count, we have truncated this section to simply indicate that an identified systematic review from the overview will be updated.

Abstract: Line 72 - 73, not clear why you're searching Embase Classic if the search is from 2008. Also please be consistent with how you report the platform. For example Ovid Medline and Wiley for CDSR is fine, but then you don't state what the platform for Embase or PsycINFO are.

Response: Thank you for your question. The Ovid platform we have access to includes both Embase Classic and Embase; we cannot search these separately. In respect of journal word count limits, this section of text has been truncated to list the databases themselves and not the interfaces used to access them.

Abstract: Line 74, please delete "to the present date" since that always changes; or replace it with a definitive data like the date of the search or a certain month.

Response: We have reworded this section to indicate that the searched will be conducted as of 2008, thereby removing any denotation of date. At this point we cannot be certain exactly when those searches will be undertaken.
Abstract: Line 81, since you are using tools for both methodological quality and risk of bias, please update the statement. For example 'methodological quality of systematic reviews, risk of bias of randomized and non-randomized trials and methodological quality of cohort studies.

Response: Changes made, as suggested.

Methods: You have reported on the reporting guidelines for this protocol, but not on the reporting guidelines that will be used for the actual review (assuming you'll be using PRISMA). Please add a statement declaring these.

Response: We have added the relevant reporting guideline for both the overview (PRIO-harms) and the updated systematic review (PRISMA) components.

Methods: For the search strategies for the overview of reviews, it is hoped that the search strategy has already been finalized and can be incorporated into the published protocol as the peer-review process may result in major changes to the concepts and syntax that will be used in the review.

Response: No changes to the search strategy are required following the peer-review process. The search strategy has been finalized and peer-reviewed using PRESS.

Methods: For the search strategy for the updated review on e-cigarettes, it's not clear if the search strategy used by the original review being updated will be used verbatim or if it will just be the basis of an updated search prepared by a member of the evidence synthesis team. Please clarify.

Response: We will evaluate the search strategy of the candidate review and make modifications as necessary (e.g., addition of MeSH terms). Additional text has been added to the manuscript for clarity.

Reviewer #1

Line 145 - may also be useful to say how many of these quit attempts were successful, if those data are available.

Response: Authors of the report do not then report how many of those quit attempts were successful. No change made to the manuscript.

Line 224 – I think it is a bit unusual to badge exercise as an 'alternative therapy' - and it seems in some places you do and in some you don't. I don't necessarily have a problem with this approach.
but the authors should confirm they are happy to categorise it in this way as that may not be the way most people in the field would categorise exercise therapy.

Response: We agree that exercise should not be grouped with alternative therapies. As this occurred only in the background section, we now present information separately for exercise and alternative therapies.

Lines 292-297 – I know further on you define which ‘benefits and harms’ you are interested in but I wonder if it’s worth specifically referring to them in your key questions? Without this it sounds vague.

Response: We would prefer to keep the questions as they are, for brevity. Readers can refer to Table 1 for the details.

Line 347 - of note, a new Cochrane handbook chapter on overviews of reviews should be out any day now

Response: Thank you. We have reviewed the chapter and no changes to the manuscript are necessary. Given that the document is not available publicly, we have not referenced it.

Paragraph starting line 356 - I’m confused about how grey literature, particularly reports of ongoing and completed studies, would fit into an overview of reviews. Do you mean ongoing and unpublished systematic reviews as opposed to studies?

Response: Thank you for pointing this out. We mean both: review for stage 1 and studies for stage 2. We have changed the text to state ‘reports’ instead of ‘studies’.

Line 396 (and throughout) – I would be a bit careful with the terminology you use to describe behaviour change techniques. I think most people reading this would assume you were referring to Michie's 93 item taxonomy which has superseded the smoking specific taxonomy, but it sounds to me like you are planning on using the smoking specific taxonomy. I think this is sensible but would re-word to make this very clear - otherwise people who see "behaviour change techniques" are going to assume you mean the 93-item taxonomy

Response: While the behavior change techniques (BCTs) covered in the 93 item taxonomy may apply, as noted in the manuscript, coding of BCTs will be guided by the taxonomy of techniques used specifically in smoking cessation interventions (Michie et al., 2011). We have tried to include the language ‘used in smoking cessation’ where relevant to be as clear as possible.

Line 404 - Are you going to go back to the individual studies to code behaviour change techniques? If not, I think it is highly unlikely you are going to get this granular info at the study
level from many, if any, systematic reviews, especially because different author teams will use different classification systems for characterising behavioural content.

Response: Thank you for considerable thought put here. We will code to the best of our ability using face-value information provided in the reviews. If not reported, we will comment on this in the overview.

Line 417 - can you really call this independent, as the second reviewer will know that the first has excluded all of the title/abstracts they are looking at?

Response: Actually, DistillerSR operates such that the second reviewer doesn’t know whether another person has reviewed it. References will be randomized and screening will be done concurrently to ensure that each reviewer cannot determine whether a given reference was excluded by another review. This information has been added to the manuscript for abundant clarity.

Line 421 - Instead of excluding where it's unclear if something should be included after duplicate review, why not refer to a third reviewer?

Response: We could certainly do this. The manuscript has been changed, accordingly.

Paragraph starting line 441 - Different systematic reviews including the exact same studies can come up with totally different conclusions. So I'm unconvinced by this approach – I think if at all possible you need to be more comprehensive or select based on methodological quality, or at a minimum compare conclusions across reviews that look at the same thing.

Response: If two reviews with the same included evidence were found but with different conclusions, then we would need to look further to see if some other factor would lead to choosing one over the other. This relates to discordance mentioned later in the protocol.

The reviewer here mentions quality, and we also mention this in the same paragraph. We acknowledge the possibility that it may be important to include both reviews if, for example, aspects of interpretation differed, to present these differences to the readership. We could look for the potential for ‘spin’. As also mentioned later in the same paragraph, the criteria will be used as a guide, and we will need to be thoughtful and thorough when potentially considering excluding reviews.

The authorship team understands that the circumstance of finding one review that supercedes all others may not be a frequent occurrence. The systematic review team will map this information carefully, review with the wider protocol authorship team, and transparently report this information to readers. We hope this instills your confidence in our intended process.
No changes made to the manuscript.

Paragraph starting line 459 - I'm not clear what the value of completing this exercise is - an extra sentence to explain might be useful

Response: Reporting the degree of overlap is recommended when overlapping reviews are included. While this does not omit potential bias caused by inclusion of overlapping reviews, it provides an indication regarding the extent of overlap. The manuscript has been edited to communicate this.

Line 483 - "Eligible reviews will be included in the overview irrespective of methodological quality" - that's not strictly true if you are excluding overlapping reviews on the basis of methodological quality

Response: We have adjusted the language in this section. In essence, we were referring to not having a threshold below which would exclude reviews and have clarified what the reviewer noted about duplicate or overlapping reviews.

Line 499 - for any meta-analysis I would also collect the number of included studies and number of participants, as well as way in which authors dealt with missing data

Response: We have updated this section to include this information.

Line 522 - may also be important to look at baseline level of nicotine dependence (either using a scale like the FTND or cigarettes per day as a proxy)

Response: Thank you for your suggestion. We have added baseline level of nicotine dependence as a subgroup variable of interest for the overview of reviews and the e-cigarette update review.

Line 558 - "...Subgroup analyses within reviews will provide direct evidence for effect modification." Consider rewording as any evidence from subgroup analyses will by its very nature be indirect evidence.

Response: We have removed ‘direct’ from the sentence.

Paragraph starting line 569 - I'm not sure how this discussion of discordance aligns with your plans to exclude overlapping reviews

Response: To the point mentioned earlier, similar reviews may have the same evidence but different results or conclusions. A further look into these reviews will be needed to tease out any potential differences (with respect to eligibility criteria, data extraction, interpretation, etc.)
resulting in discordant results or conclusions and whether the focus should be on one of the reviews.

We have further clarified the relationship between overlap detection and discordance analysis at the end of the section on overlap detection.

Paragraph starting line 598 - Just a note that I would exercise caution comparing GRADE across reviews as GRADE is inherently subjective, so I wouldn't treat it like a consistent measure across reviews

Response: Thank you for raising this, and we had not addressed this specifically in our protocol. We feel that it will be important to look at how reviews graded their information as this forms the basis of interpretation. Although subjective, if two reviews come to the same grading/conclusion, then there is a measure of robustness; if they don’t, then understanding where those differences lie (where possible/reported) will be important to highlight to the reader why there is variation in interpretation. If such discordance is unclear, then we simply provide this information to the reader. We hope this helps to instill your confidence in our process.

Line 629 - Why not just prefer biochemically validated data and only extract self-report where validated is not available?

Response: We feel that extracting all will be important to inform the analyses and interpretation that can be undertaken. If, for example, there were fewer biochemically-validated studies and much more on self-report, it would still be important for decision-makers to see that evidence. The trade-off might be greater precision for one with an inherent greater risk of bias compared with less precision for another but at a lesser risk of bias. Presenting and interpreting that information would still be important for the reader. And perhaps there might be consistency of results between the two, which can speak to the robustness of the conclusion. One point to keep in mind is that evaluations of bias can only lend to ‘risk of’, not that it is absolutely occurring. No changes were made to the manuscript.

Line 635 - Will you be assessing risk of bias for all studies (incl. previously included ones) or for new studies only? If the latter, use the methods of the candidate review for easier comparison?

Response: Thank you for raising this. For consistency, we will assess risk of bias for all studies including those previously included in the original review. We will also consult studies included in the original review to ensure that all outcomes of interest have been captured. Text has been added to the manuscript for clarity.

Line 670 - you may also want to look at cigarettes per day at baseline, motivation to quit, and in prospective cohort studies in particular previous use of EC
Response: Thank you. We have added baseline level of nicotine dependence as a subgroup variable of interest.

We have decided to not include motivation to quit as a subgroup variable as there is evidence to suggest that motivation may not be integral to quitting. Further, it would be difficult to apply motivation to quit to guideline recommendations.

After careful consideration, we have decided to make changes to eligible study designs for the updated review on e-cigarettes. For harms outcomes, we will consider randomized and non-randomized controlled trials as well as comparative observational study designs. However, for outcomes related to benefits, we have decided to restrict inclusion to randomized controlled trials. The Task Force very rarely considers non-randomized trials and observational studies for benefits. These study designs are prone to bias – those participants using e-cigarettes may be wanting to quit tobacco smoking while those not using e-cigarettes may not be intending to quit, for example. Given this change, we will not perform subgroup analysis by previous e-cigarette use.

Tables - comparator - may need to be careful as what some studies call "usual care" others would call an intervention

Response: Thank you for raising this point, and we agree. We have included this for the reason of being inclusive. We plan to provide specification, where reported, of what those comparator groups were comprised of when presenting and synthesizing information for readers.

Tables- outcomes – I am not clear on the rationale for including reduction in tobacco smoking as an outcome. There is no evidence to suggest reduction without quitting improves health outcomes.

Response: As there is evidence to suggest that reduction in tobacco smoking may lead to complete cessation and may have health benefits, it was considered as a potential outcome of interest for the review. It was subsequently rated as an important outcome by both the Working Group and patients and therefore included in the review. No changes made to the manuscript.

Tables- outcomes - you specify that you are only going to look at adverse events due to treatment as defined in a given review. This might be a bit risky and if possible I would recommend looking at adverse events overall, as well, as with things like EC there is no consensus on what AEs are caused by treatment and what ones aren't, and the definitions may vary substantially based on the allegiances of the original study/review authors

Response: Thank you for your suggestion. We agree that limiting to ‘treatment-related’ adverse events may be problematic for the reasons mentioned. We will consider all adverse events. Tables 1-3 and Figure 1 have been changed accordingly.
Table 2 - intervention - why are you not including interventions to promote gradual cessation? I don't necessarily disagree with this approach but think you need to justify it.

Response: We will consider interventions that promote both abrupt and gradual tobacco smoking cessation. Tables 1 and 2 have been edited accordingly.

Figure 1- again question including smoking reduction as an outcome

Response: As above.

Figure 1- again question only looking at AEs due to treatment

Response: Thank you. As mentioned earlier, we will now consider all adverse events. Figure 1 has been changed accordingly.

On a last note, if the review you choose to update for electronic cigarettes ends up being a Cochrane update, please do feel free to be in touch with us at the Cochrane Tobacco Addiction Group (you can email me directly on Jamie.hartmann-boyce@phc.ox.ac.uk) as we were considering an update of this review to start in the new year, and there may be efficiency savings that could be made.

Response: Dr. Hartmann, we very much appreciate your offer and would gladly get in touch at that juncture.

Reviewer #2

This systematic review protocol is very well-written and nicely lays out all methodologic considerations and plans. The protocol provides both definitive, a priori decisions for certain procedures and explains where flexibility will be required based in the identified evidence. My biggest concern, quite frankly, is the overlap between this work and our current update (using similar methods) that is underway for the U.S. Preventive Services Task Force (https://www.uspreventiveservicestaskforce.org/Page/Document/final-research-plan/tobacco-smoking-cessation-in-adults- including-pregnant-women-interventions). While our scope and methods are different in some cases (e.g., we have a broader scope in terms of including primary care referable interventions [e.g., MI interventions, stage-based approaches, incentive-based interventions]; our search was limited to 2014 to 2018, our review on ENDS evidence is solely based on a synthesis of primary evidence not bridging an existing review), my guess is that we'll have extremely similar included bodies of evidence and conclusions. I can reach out separately to share our progress to-date and brainstorm potential collaboration.

Response: Thank you for reaching out separately. We look forward to continued discussions.
Objective and Key Questions: Here or elsewhere, you may want to provide rationale for choosing the overview of reviews methods (proliferation of trial evidence AND reviews [our existing review of reviews identified over 50 reviews synthesizing over 800 trials] and the general existing consensus by other guideline-making bodies that stop smoking interventions "work".

Response: Great suggestion. We have made this change to the manuscript.

Stage 1: Throughout the methods, I appreciate that you thoughtfully laid out all potential methodological options and rationale (e.g., for handling overlapping bodies of evidence, for handling discordant findings) and your proposed procedures related to each option/method.

Response: Thank you.

Stage 1: Searches: 2008 to current date. It would be nice to see rationale for choosing to go back so far in time (my guess is 10 years) given the overview of review methodology and your plans for handling overlapping bodies of evidence. As you are probably aware, there are literally hundreds of systematic reviews published since 2008 that will likely meet your criteria and will contain considerable overlap. The burden of mapping this evidence is considerable. I think you should strongly consider a shorter time frame for your searches (5-7 years versus 10?) and only go further back in time if you determine that a review is lacking for a particular category of intervention or particular population of interest. I think it's extremely defensible given that we've already published (as has Cochrane for drug studies) more recent overviews of reviews. Else, we have numerous Excel spreadsheets that already examine the overlapping literature in these reviews if you do not want to re-create or use as a starting point.

Response: We appreciate this important feedback. The decision to begin searching from 2008 was based on suggestion from a clinical expert as well as a scoping exercise of available Cochrane systematic reviews. Through the scoping exercise, we located at least one review produced in 2010 which has yet to be updated (i.e., Cochrane review on hypnotherapy). Given this information, we decided that searching for reviews produced in the last 10 years was sensible. While we appreciate the amount of work this entails, we would prefer to use a single search strategy to identify reviews and then address overlap using the approach outlined in the manuscript. We very much appreciate the offered resources. No changes made to the manuscript.

Stage 1: Pg. 21, lines 459-468: I did not fully understand the "correction" that is made when applying the CCA method. First, I'm not clear why "cases where overlapping data ...cannot be avoided". Is there some threshold by which you'll determine the overlap to be "considerable" such that one reviews "trumps" another? What if the difference is only 3 studies and it's defensible based on that review's inclusion/exclusion criteria? Second, the CCA "correction" needs further explanation. Where is the correction factor going if you're just reporting the effect estimates as reported by the included reviews? Is this really just a value that's reported to give the
reader a sense of the overlap of the included bodies of evidence? I'm having a hard time figuring out how this is really a correction in a statistical sense.

Response: Ideally, we would like to minimize overlapping reviews by excluding those which are superseded by a more recent, comprehensive, or higher quality review. In the example provided, we would select the review that has the greater number of studies for a given PICOTS, even if the difference is only 3 studies (as long as the reviews have similar search dates and are of similar methodological quality).

Inclusion of overlapping reviews may be necessary, for example, in the case of reviews with similar search dates, quality, and comprehensiveness. When overlapping reviews are included in an overview, it is recommended to report the degree of overlap. The CCA method simply provides an estimate of the degree of overlap across reviews with a value of 0-5 suggesting slight overlap, 6-10 moderate overlap, and >15 a very high degree of overlap. It is not a statistical correction for bias.

In response to another reviewer, we have included the formula for calculating CCA.

Stage 1: You may also want to discuss how you will handle selection of other published overviews of reviews. We have come across a LOT of these in our update. Will you just exclude them (and check their included reviews) because they do not meet your definition of a systematic review? But, it looks like you do plan to include network meta-analysis?

Our intent is to use any existing overviews as a supplemental source for identifying additional reviews.

Response: We would be willing to include overviews that conduct network meta-analyses only with the explicit declaration that the overview authors themselves were familiar with the primary studies to ensure that they were similar enough to include in the network (transitivity assumption). We have made this change to the manuscript.

Stage 1: For KQlc, it would be nice to see if you have criteria for evaluating the credibility of reviews' subgroup analyses (meta-regression, stratified analysis).

Response: Thank you for raising this point. We will use the GRADE criteria for evaluating the credibility of subgroup analyses. This has been added to the manuscript.

Stage 1: Can the first 2 I/E tables be combined? It seems like the only difference is the latter looking for evidence on effective BCTs (reviews limited to specific BCTs or reviews that provide evidence of effect modification). I think it would be easier on readers to combine the two tables and include the extra information in the Intervention row in the 2nd table in the 1st.
Response: Given important differences in eligible interventions and comparators between KQ1a/b and KQ1c, as well as differences regarding the selection process (i.e., flexibility in terms of eligible interventions and settings for KQ1c), we would prefer to keep the tables separate.

Stage 1: There are many published reviews that limited their inclusion to a specific subpopulation (e.g., young adults, racial/ethnic minorities, smokeless tobacco users); I would suggest commenting on how these will be 'included' or otherwise incorporated into your synthesis.

Response: Yes, in the subgroup section we acknowledge that some of the subgroup factors may indeed comprise the scope of a particular review. We further state that we will provide the appropriate statements relating to interpretation but would be unable to perform comparisons across reviews in absence of direct familiarity with the primary studies. No changes made to the manuscript.

Stage 1: Finally, Cochrane keeps a very nice spreadsheet of their tobacco reviews and their plans and timelines for updating each review. They have shared a copy with us and would likely do the same for you. It's nice to see where updates are planned such that you don't go through a lot of work abstracting one review that is planned for an update during your review time frame.

Response: Thank for you letting us know. We can check into this.

Stage 2: For I/E setting: Many of these studies will take place "In" research settings -- literally academic research settings recruiting smokers through mass advertising. Will studies in these "community" or research settings be included?

Response: Great point. Because participants are recruited from the community, we don’t think these studies are different in terms of relevance to the guideline from those in primary care settings. We will include studies in academic research settings. The eligibility criteria has been updated accordingly.

Citations: Citation 91 (Balshem): Do you mean to cite the AHRQ RoB paper (https://effectivehealthcare.ahrq.gov/topics/methods-bias-update/methods} or the Balshem paper on outcome analysis reporting bias in grey literature?

Response: The reference we have cited is correct. That article was dually about finding grey literature and then assessing selective reporting and analysis bias for the evidence as a whole (looking across published and grey literature documents to make that determination). A co-author of this protocol is a co-author of that guidance (A Stevens).
Citations: Citation 95 (Fu) has been updated and is published on AHRQ's website (https://effectivehealthcare.ahrq.gov/topics/methods-quantitative-synthesis-update/methods).

Response: Thank you for notifying us. The updated version is now cited.

Reviewer #3

Section: Stop Smoking Interventions. The division of approved pharmacotherapies into OTC and non-OTC is not a typical approach to smoking cessation pharmacotherapies. Also, the inclusion of cytisine (a natural health product) is to be questioned since it is not routinely used by most clinicians and unlikely to have been included in any systematic reviews published to date.

Response: For the final report, interventions will not be bannered according to access. However, for the background, we felt that indicating route of access would be important context for the reader.

Any potentially effective product should be evaluated in context of the review. The guideline will help to education primary care clinicians on what options are available. A finding of a lack of evidence is still an important finding.

Section: Stop Smoking Interventions 2. Line 160: I would suggest also adding that role of Varenicline is to relieve cravings.

Response: Thank you. We have added this.

Section: Stop Smoking Interventions 3. Line 163: It would be helpful to add a sentence about mechanism of action of Bupropion to keep this section consistent.

Response: Thank you. This has been added.

Section: Stop Smoking Interventions 4. Line 222: Section on alternative therapies is very vague with only names of therapies provided. It does not seem to follow as well from previous sections. I would suggest deleting this section or mentioning which therapies will not be included in this systematic review. St. John's wort is not intended for smoking cessation so unusual herbal product to include.

Response: Thank you. We have expanded the section on alternative therapies to include potential mechanisms of action. Information on eligible interventions appears in the methods section of the manuscript.
Although not approved as a smoking cessation aide in Canada, we decided to include St. John’s wort due to ease of access and because it has been examined as a cessation aid in clinical trials and included in previous reviews. This justification can be found in the methods section of the report.

Section: Objective and Key Questions General comment: I would recommend stating clearly which "stop smoking interventions for adults" will be included in this review. These details are mentioned in table 1 but would help the reader focus in on what will be included. Also, please clarify if special populations will be included like pregnant women.

Response: We have added the broad classifications that will be covered and an indication of the subgroup populations of interest.

Section: Objective and Key Questions - I am not sure why on line 287, it states "If feasible, the overview will also evaluate the benefits and harms of behavioural change techniques .."

Response: Behavioural interventions are, in essence, multifaceted in that they are comprised of various components: intensity of delivery, frequency of delivery/receipt, how contact is made with the recipient, the type of intervention provider, and the content that is delivered. Key question 1c focuses on the content. While key questions 1a/b are intended to evaluate the effectiveness of such interventions (e.g., does brief advice work?), the intent of key question 1c is to determine the effectiveness of specific techniques used within these behavior change interventions (e.g., does advising about the health consequences of smoking work?).

As we are currently unaware of the volume of literature on the effectiveness of behavior change techniques, we will evaluate the feasibility of undertaking key question 1c following full-text screening.

No changes made to the manuscript.

The process for dealing with overlapping systematic reviews is appropriate given that multiple reviews have been published on smoking cessation interventions and choosing the highest quality review will be challenging.

Response: Appreciate your comment here. We are aware that it may be infrequent that we find one review that would trump all others. No changes made to the manuscript.

With respect to assessing the quality of the body of evidence - on line 607, it states "we will not consult primary studies for the purpose of conducting GRADE assessments". This approach will limit the ability to provide an accurate GRADE assessment for some of the reviews published. However, high quality reviews should have included their own quality assessments which should be available for review.
Response: We hope to be able to draw from existing GRADE assessments in reviews. Where not existing, the decision to undertake GRADE assessments with face-value information was made in consideration of feasibility and practicality. No changes made to the manuscript.

Reviewer #4

General comments. Overall well written and the article is easy to follow.

Would suggest that you state the objectives of this article (protocol for 2 systematic reviews) as the beginning of the article. It's not clear that this article is a protocol until halfway through reading it.

Response: We have added text to make this clearer in the abstract and the ‘Objective and Key Questions’ section. Thank you.

The first systematic reviews of various stop smoking interventions seem to be somewhat over ambitions. Key questions are broad and do not convey enough specificity to what exactly you will be looking for.

Response: We are concerned that the type of information that would need to be added to the text of the key questions for further specification would make them overly long and cumbersome to read. In response to another reviewer, we have added information to the Objective section that precedes the listing of the questions. We feel that readers can otherwise consult Table 1 for full specification of the details.

A lot of emphasis is placed on behavioural therapies and the proposed subanalysis of behavioural change techniques (Key Question lc) could be its own paper. Would consider writing a 3rd paper with this question only.

Response: Keeping all objectives together will help to easily link between the final guideline that is produced and the evidence that was developed to underpin it. This would be in keeping with the needs and purposes of the Task Force. No changes made to the manuscript.

Pharmacotherapies interventions are not given as much attention. Are you looking at the individual treatments, or are you going to group them all together?

Response: We will include all relevant treatments according to how they are analyzed in the systematic reviews, whether individually or in combination. We will comment on the applicability of the evidence in the final review report. No changes made to the manuscript.

Except of a brief paragraph on alternative therapies in the background sections, nothing specific mentioned in method section.
Response: We are relying on the background section and Table 1 inclusion and exclusion criteria as providing the relevant information to understand the context of the topic. Only where needed in relation to specific methodological approaches did we call out aspects of that intended scope in the methods section. No changes made to the manuscript.

Will you be looking at synergistic/additive effects of combining different treatment together?

Response: This could be a point to bring up in our discussion of the results, but will likely not be something we can actually undertake. This would be due to our reliance on how authors have analyzed those studies and reported the findings, coupled with the inability to undertake informal indirect comparisons (for reasons outlined in the manuscript). No changes made to the manuscript.

The e-cigarette literature is fairly young and though more information is being added daily, the number of e-cigarette systematic reviews maybe limited and not very informative. An actual systematic review of recent publications would provide better insight on the benefit and harms of e-cigarettes to promote cessation of tobacco smoking among adults.

Response: Yes, we plan to update an existing systematic review for the reasons you have noted, to ensure this evidence base is as up-to-date as possible. Thank you for your comment. No changes made to the manuscript.

Abstract: The Method section is too long and contains too many details. This subsection should be cut down.

Response: We have edited the abstract section.

Abstract: It is clear that two systematic reviews will be conducted: 1) various stop smoking interventions, 2) e-cigarettes. The methods described for the reviews are intermixed and it gets confusing what will be done for each review. It would be clearer if a separate method paragraph would be written for each review.

Response: We have detailed the various methods the apply to each review type. Where there are commonalities, to conserve on space, we have made a link in the second review’s methods to connect it with the first. No changes made to the manuscript.

Background: Overall the Background section is well written. It highlights the health and economic impact of smoking and the benefits of quitting. It also described the different smoking cessation therapies clearly.

Response: Thank you.
Background: Many of the statistics referenced seem out of date (2012). Please replace with more up to date statistics.

Response: Where possible, we have now included statistics from the 2017 Canadian Tobacco, Alcohol and Drugs Survey.

In some cases, we could not provide more recent data. A few of the 2012 statistics are from two recently produced reports:


Background: The word "prevalent" is over used in the Prevalence and Burden of Tobacco Smoking section. Please consider combining sentences and rewording slightly.

Response: Thank you for noting this. We have revised.

Background: Line 139: consider rewording "Stopping smoking reduces the risk..." to "Stopping to smoke reduces the risk...".

Response: We have addressed your comment in context of another reviewer’s comment. Thank you for raising.

Background: Line 147-148: Sentence on e-cigarette use out of place with tone of paragraph. Sentence should be on increase e-cigarette use to quit.

Response: Thank you. We have replaced prevalence of use data with the proportion using e-cigarettes as a cessation aide. This better aligns with the intent of the paragraph.

Background: Line 151: Would consider removing this sentence. Redundant when considering the information provided within the rest of the paragraph.

Response: Thank you. We have struck this sentence.

Background: Line 226: Sentence on St. John's Wort seems out of place. You are talking of its alternate use as an antidepressant and it's not clear that it is use as a smoking cessation aid.
Response: Thank you. We have added text to make this clearer.

Literature search: Why is PubMed not one of the databases being searched?

Response: To address this question, we have consulted with our senior information specialist. Given redundancies across PubMed and the databases we plan to search, it is unlikely that we will miss eligible reviews/studies by not searching PubMed. We also perform a prepublication update which will account for any delays in indexing.

Data mapping and overlap detection: What will you do to address overlapping systematic reviews that have conflicting conclusion using the same data pool?

Response: We will need to explore reasons as to why conclusions are conflicting (see section on ‘Discordance’). For example, it could be due to the inclusion of different evidence or differences in how the data were interpreted. We will make this information transparent to the reader.

Discussion: Would considering including 2-3 sentences on the importance of these reviews and the health and economic impact of their findings.

Response: We have added information to this regard. Thank you.

Tables and Figure: Clear, easy to understand and follow.

Response: Thank you. No changes applicable to the manuscript.